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PATHOGENESIS OF BUNDLE BRANCH BLOCK

REVIEW OF THE LITERATURE, REPORT OF SIXTEEN CASES WITH
NECROPSY AND OF SIX CASES WITH DETAILED HISTOLOGIC
STUDY OF THE CONDUCTION SYSTEM

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WASHINGTON, D C

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INTRODUCTION

The original concept of the electrocardiographic manifestations of
bundle branch interruption, as developed by Eppinger and Rothberger ¹
(1910) and confirmed by Rothberger and Winterberg ² (1913), Lewis ³

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From the Georgetown University School of Medicine and the Army Medical
Museum

1 Eppinger, H, and Rothberger, C J Ueber die Folgen der Durch-
schneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr f klin
Med **70** 1, 1910

2 Rothberger, C J, and Winterberg, H Zur Diagnose der einseitigen
Blockierung der Reizleitung in den Tawaraschen Schenkeln, Zentralbl f Herz-
krankh **5**:206, 1913

3 Lewis, T Spread of the Excitatory Process in the Vertebrate Heart,
I-V, Phil Tr Roy Soc, London **207** 221, 1916

(1916), Wilson and Hermann⁴ (1921) and others, has been attacked in the past few years to the extent that the term right bundle branch block has been changed to left bundle branch block and vice versa. The main mass of evidence in favor of the original concept was accumulated as the result of experiments on animals, mainly dogs, in which interruption of part or all of one or the other bundle branch, usually by surgical section, was produced in a normal heart. The diagnosis of bundle branch block was then applied to conditions studied in the clinic in which the electrocardiograms resembled those made experimentally.

RESULTS OF PHYSIOLOGIC EXPERIMENTS ON BUNDLE BRANCH BLOCK

When a bundle branch is cut artificially there results an increased amplitude of the ventricular deflections, a preponderance of the ventricle containing the nonintact bundle branch, an increased spread of 0.03 to 0.04 second in the QRS complex, with notching of that complex, and opposition in direction of the T wave to that of the main ventricular complex. There is a difference, however, between the electrocardiographic picture produced by section of a bundle branch in the dog and the electrocardiographic picture assumed by analogy to represent pathologic interruption of the bundle branch in the human heart. In the dog the chief initial deflections are usually in the same direction in the three conventional leads, and the experimental picture is termed concordant. In man, however, the electrocardiographic picture which typifies bundle branch block is usually of the discordant form, i. e., if the chief initial complex is upright in lead I, it is down in lead III, whereas in lead II it may be upright, down or biphasic. This difference is explained by the differences in the anatomic course of the left bundle branch, the axis and position of the heart, the shape of the heart and the thickness of the two ventricles.

In man the criteria established by Carter⁵ (1914) for the diagnosis of bundle branch block were as follows: (1) widening of the QRS complex beyond 0.1 second, with notching, (2) preponderance of the ventricle with a healthy bundle branch, i. e., right or left axis deviation, as the case might be, or, in other words, the dextrocardiogram with left bundle branch block and the levocardiogram with right bundle branch block, (3) exaggeration of the amplitude of the ventricular deflections (QRS and T), (4) the T wave directed oppositely to the initial ventricular deflection. If the initial ventricular deflection was upright in lead I

4 Wilson, F. N., and Hermann, G. R. An Experimental Study of Incomplete Bundle-Branch Block and of the Refractory Period of the Heart of the Dog, *Heart* 8:229, 1921.

5 Carter, E. P. Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle. A Report of Twenty-Two Cases in Which Aberrant Beats Were Obtained, *Arch. Int. Med.* 13:803 (May) 1914.

and downwardly directed in lead III, right bundle branch block was assumed to exist, if it was down in lead I and upright in lead III, left bundle branch block was predicated. The former was much more commonly observed in studies of patients than the latter. This concept was in perfect accord with contemporary concepts of ventricular preponderance and premature contractions.

As early as 1920, however, Fahr,⁶ on purely theoretic grounds, expressed doubt as to the validity of the interpretation of bundle branch block, as well as the curves indicating ventricular preponderance, and suggested that the terms right and left should probably be interchanged. The same year Oppenheimer and Pardee⁷ stated that they found the interrupting lesion in the branch opposite the one anticipated when they examined two hearts histologically.

In 1930 more serious doubt began to develop in America regarding the accuracy of interpretation as to which is the levocardiogram and which is the dextrocardiogram in the case of the human being when Barker, Macleod and Alexander⁸ published curves exactly opposite to those previously obtained for animals. These writers were able by a fortunate circumstance to make electrocardiograms of extrasystoles (ectopic contractions) produced by stimulating directly the exposed heart of a human subject. Wilson and these original investigators⁹ suggested that the common type of bundle branch block (formerly called right bundle branch block) is in reality due to obstruction of the excitation wave along the left bundle branch, whereas the unusual variety (the reverse picture electrocardiographically) is due to a block of the right bundle branch.

Later, Marvin and Oughterson¹⁰ (1932) and Vander Veer¹¹ (1933) made similar observations on exposed human hearts and in general confirmed the results. However, Lundy and Bacon¹² (1933),

6 Fahr, G. An Analysis of the Spread of the Excitation Wave in the Human Ventricle, *Arch Int Med* **25** 146 (Feb) 1920.

7 Oppenheimer, B. S., and Pardee, H. E. B. The Site of the Cardiac Lesion in Two Instances of Intraventricular Heart Block, *Proc Soc Exper Biol & Med* **17** 177, 1920.

8 Barker, P. S., Macleod, A. G., and Alexander, J. The Excitatory Process Observed in the Exposed Human Heart, *Am Heart J* **5** 720, 1930.

9 Wilson, F. N., Macleod, A. G., and Barker, P. S. The Order of Ventricular Excitation in Human Bundle-Branch Block, *Am Heart J* **7** 305, 1932.

10 Marvin, H. M., and Oughterson, A. W. The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricles, *Am Heart J* **7** 471, 1932.

11 Vander Veer, J. B. Premature Beats Produced by the Mechanical Stimulation of the Exposed Human Heart, *Am Heart J* **8** 807, 1933.

12 Lundy, C. J., and Bacon, C. M. Premature Left Ventricular Beats from Electrical Stimulation of Exposed Human Heart, *Arch Int Med* **52** 30 (July) 1933.

in the same type of experiments, found that when the apical region of the left ventricle was stimulated the extrasystoles confirmed the new conception but that when the basal region of the left ventricle was stimulated the major deflection was upright in lead I. Also, Prinzmetal, Oppenheimer and Dack¹³ (1937), stimulating electrically the upper lateral region of the left ventricle of the exposed heart of a patient with constrictive pericarditis whose electrocardiograms showed right axis deviation due to displacement of the right ventricle forward and to the left, obtained extrasystoles with a small upright main complex in lead I and a large upright main complex in lead III, whereas, after closure, when they tapped the thin thoracic wall overlying the right ventricle at four different points, they found the main ventricular deflection of the resulting extrasystoles inverted in lead I and upright in lead III in 3 instances and the reverse in the fourth instance. These authors concluded that the new conception can be safely applied only in the presence of a normal electric axis or of left axis deviation. They were aided in this belief by experimental work performed on cats by Abramson and Weinstein¹⁴ (1936), who showed that the direction of the major ventricular complex in lead I changes at a line of transition which does not strictly divide the left from the right ventricle and that a shift in this line of transition occurs with rotation of the heart and alteration of the electric axis.

Wilson, Macleod and Barker⁹ (1932) soon fortified the new terminology which had been proposed by using semidirect leads for dogs in which one or the other bundle branch had been severed and by stimulating the ventricles separately with an exploring needle held close to the surface.

About the same time Roberts, Crawford, Abramson and Cardwell¹⁵ (1932), in experiments in which they divided the bundle branches in cat hearts, obtained both concordant and discordant curves in which when the right bundle branch was cut the chief initial deflection was downward in both types, but in lead III the deflection was upward in the discordant type. After the left bundle branch was cut, exactly opposite results were obtained. These results indicated to them that the important lead to study for determining the location of the lesion is lead I.

13 Prinzmetal, M., Oppenheimer, B. S., and Dack, S. Localization of Ventricular Extrasystoles in a Human Heart with Right Axis Deviation, *J. A. M. A.* **108** 620 (Feb. 20) 1937.

14 Abramson, D. I., and Weinstein, J. A Basis for the Analysis of Variations in the Form of Electrocardiographic Curves Resulting from Experimental Premature Contractions, *Am. J. Physiol.* **115** 569, 1936.

15 Roberts, G. H., Crawford, J. H., Abramson, D. I., and Cardwell, J. C. Experimental Bundle-Branch Block in the Cat, *Am. Heart J.* **7** 505, 1932.

By means of a method of analyzing the electrocardiogram by a fusion of the three leads into a single curve, or monocardigram, Mann¹⁶ (1931) was able to show that with right bundle branch block the electrocardiogram has an inverted main deflection in lead I, while with left bundle branch block the main deflection is upright in lead I. As early as 1920 Mann¹⁷ had concluded that the original terminology for bundle branch block was incorrect.

In human beings for whom a diagnosis of bundle branch block had been made, Nichol¹⁸ (1933) found that in instances in which the chief initial deflection was up in lead I and down in lead III (right bundle branch block, original terminology) the subclavian pulse was definitely delayed, and he concluded that the curves really signified left bundle branch block.

By means of serial precordial leads Wilson, Johnston, Hill, Macleod and Baiker¹⁹ (1934), for patients who showed electrocardiographic curves which were formerly said to typify left bundle branch block, obtained curves in which the lead from the right side of the precordium showed a late chief upstroke, whereas the lead from the left side of the precordium showed an early chief upstroke approximately synchronous with the peak of R in lead I. These curves were strikingly similar to those which they obtained by the same method of leading after section of the right bundle branch in dogs.

Wolferth and Margolies²⁰ (1935), by studying graphically the time relations of various events associated with right and left ventricular contraction shown by a series of patients whose electrocardiograms conformed rigidly to accepted criteria for the common type of bundle branch block, found that ejection from the left ventricle was significantly delayed. Checking the methods employed by Wolferth and his co-workers, Katz, Landt and Bohning²¹ (1935) urged caution in draw-

16 Mann, H. Interpretation of Bundle-Branch Block by Means of the Monocardigram, *Am Heart J* **6** 447, 1931.

17 Mann, H. A Method of Analyzing the Electrocardiogram, *Arch Int Med* **25** 283 (March) 1920.

18 Nichol, A. D. The Interpretation of Lead Inversion in Bundle-Branch Block, *Am Heart J* **9** 72, 1933.

19 Wilson, F. N., and others. The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead I, *Am Heart J* **9** 459, 1934.

20 Wolferth, C. C., and Margolies, A. Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block. Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, *Am Heart J* **10** 425, 1935.

21 Katz, L. N., Landt, H., and Bohning, A. The Delay in the Onset of Ejection of the Left Ventricle in Bundle-Branch Block, *Am Heart J* **10** 681, 1935.

ing such definite conclusions and pointed out that an interval of more than 0.18 second from the beginning of the QRS complex to the onset of ejection of the left ventricle, as given by the rise of the subclavian arterial pulse, suggests the probable presence of delay or obstruction of the impulse along the left bundle branch but does not exclude the simultaneous presence of depression of function of the right bundle branch. They concluded that the direction of the QRS complex is determined by other factors besides the block and cannot be used to locate the bundle branch involved in cases of intraventricular block. They suggested describing intraventricular block as (1) a common bundle branch type, (2) an uncommon bundle branch type or (3) an indeterminate type.

Kountz, Prinzmetal, Pearson and Koenig²² (1935) cut the bundle branches of revived human hearts and found that a lesion of the right bundle branch was characterized by a deflection that was downward in lead I and upward in lead III, and that section of the left bundle branch produced the opposite picture. Also, with the heart in normal position they found that extrasystoles were similar to those described by Barker, Macleod and Alexander.

By artificial stimulation of the endocardium of the ventricles of the dog, Marcou²³ (1936) regularly produced extrasystoles with images the reverse of those originally designated as showing premature contractions of the left and right ventricles, usually the curves were of the discordant type, but occasionally they were of the concordant type of Rothberger and Winterberg²⁴.

Because of the mass of experimental evidence that has accumulated, most American cardiologists have accepted the new terminology for the classic electrocardiographic curves designated as typical of bundle branch block. There are still, however, many types of electrocardiographic curves suggestive of bundle branch block but not typical of either classic left or classic right branch block. These undoubtedly represent instances of intraventricular block, but the exact mechanism of their production and the pathogenic factors are in doubt.

Apparently most European cardiologists still use the original terminology. Rothberger²⁵ has been the main champion of this school of

22 Kountz, W. B., Prinzmetal, M., Pearson, E. F., and Koenig, K. F. The Effect of Position of the Heart on the Electrocardiogram. I. The Electrocardiogram in Revived Perfused Human Hearts in Normal Position, *Am Heart J* **10** 605, 1935.

23 Marcou, I. Experimental Extrasystoles Elicited Through Artificial Stimulation of the Endocardium of the Dog, *Am Heart J* **12** 301, 1936.

24 Rothberger, C. J., and Winterberg, H. Experimentelle Beiträge zur Kenntnis der Reizleitungsstörungen in den Kammern des Säugetierherzens, *Ztschr f d ges exper Med* **5** 264, 1916.

25 Rothberger, C. J. Zur Diagnose des Schenkelblocks, *Ztschr f klin Med* **123** 460, 1933.

thought In 1933 he published an extensive dissertation on the subject in which as a result of numerous animal experiments and with the aid of Mahaim's²⁶ histologic studies he defended the original concept However he stated that the only way to settle the question to the satisfaction of all is by means of expert, systematic histologic studies of the entire conduction system of the hearts of patients whose electrocardiograms showed evidence of bundle branch block

TYPES OF CURVES DESIGNATED BY VARIOUS AUTHORS AS INDICATING INTRAVENTRICULAR AND BUNDLE BRANCH BLOCK

Confusion exists with reference to the exact significance of various aberrant forms of the ventricular complex, although most of them are assumed to be due to intraventricular block In 1911 Lewis²⁷ called attention to anomalous electric complexes accompanying the ventricular contractions of premature beats arising in the auricle in some cases He said he considered these changes due to disturbances of conduction in the smaller branches of the conduction system and called the anomalous beats aberrant He stated, "There seems every prospect that, if this hypothesis be correct, it will be possible ultimately to identify lesions which affect not only the main divisions but the smaller branches of the auriculo-ventricular bundle The products of asphyxia probably act in a selective manner upon the special tissues which serve the function of conducting impulses from auricle to ventricle" In 1912 Mathewson²⁸ reported 4 cases in human beings of bundle branch block conforming to the criteria established by Carter⁵ for this condition in 1914, when he reported 22 cases Since that time numerous reviews of series of cases have been published, which will be briefly discussed later The criteria established by Carter, already noted, were widely accepted and remained for many years the basis of the clinical diagnosis of bundle branch block

In 1917 Oppenheimer and Rothschild²⁹ described an electrocardiographic curve of a different kind which they attributed to defects in intraventricular conduction due probably, in their opinion, to lesions of the finer ramifications of the conduction system, especially in the left ventricle They coined the term aiborization block In this curve there is low rather than large amplitude of the ventricular complex, and

26 Mahaim, I Les maladies organiques du faisceau de His-Tawara, Paris, Masson & Cie, 1931

27 Lewis, T Observations upon Disorders of the Heart's Action, Heart **3** 279, 1911

28 Mathewson, G D Lesions of the Branches of the Auriculo-Ventricular Bundle, Heart **4** 385, 1912

29 Oppenheimer, B S, and Rothschild, M A Electrocardiographic Changes Associated with Myocardial Involvement, J A M A **69** 429 (Aug 11) 1917

there is increased duration of the QRS complex, which is slurred or notched in its main deflection, while there is no constant directional relation between the QRS complex and the T wave. There were many adherents to this conception, but latterly the idea has been abandoned by most workers, and the exact anatomic cause of such conduction disturbances remains unsettled. In 1919 Willius³⁰ reported under the title "Arborization Block" a series of 138 cases in which this type of curve was obtained, but several years later he stated that he had concluded that the use of this anatomic term is not justified.

In 1919 Wedd³¹ discussed the clinical significance of slight notching of the R wave as observed in 30 cases. He said he believed this change to be due to myocardial disease with defective conduction. Willius³² (1920) said he considered notching and slurring of the QRS complex in isolated derivations of the electrocardiogram to be graphic entities probably indicative of local disorders of the ventricular myocardium affecting the conduction system.

In a classic paper entitled "Bundle Branch Block and Arborization Block," Wilson and Herrmann,³³ in 1920, on the basis of animal experiments and clinical studies said they had concluded that "complete bundle branch block produces characteristic changes in the form of the ventricular complex both in animals and in man." They said they considered Carter's criteria correct for man. They concluded further, however, as follows: "Delayed conduction of the impulse through the branches of the His bundle (incomplete bundle branch block) produces ventricular complexes which are transitional in form between the normal ventricular complex and complexes characteristic of complete bundle branch block." At the same time they found little experimental evidence to indicate that lesions of the subdivisions of the bundle branches or their arborizations are the cause of "arborization block."

From 1920 to 1930 little was accomplished in the furtherance of fundamental knowledge concerning disturbances of intraventricular conduction, although many fine articles were published on the clinical significance of the electrocardiographic curves described in the earlier years. As previously mentioned, there was no unanimity of opinion even in this period concerning the question of right and left as applied to curves in cases of bundle branch block. The experiments, in 1930,

30 Willius, F. A. Arborization Block, *Arch Int Med* **23** 431 (April) 1919.

31 Wedd, A. M. The Clinical Significance of Slight Notching of the R-Wave of the Electrocardiogram, *Arch Int Med* **23** 515 (April) 1919.

32 Willius, F. A. Observations on Changes in Form of the Initial Ventricular Complex in Isolated Derivations of the Human Electrocardiogram, *Arch Int Med* **25** 550 (May) 1920.

33 Wilson, F. N., and Herrmann, G. R. Bundle Branch Block and Arborization Block, *Arch Int Med* **26** 153 (Aug.) 1920.

of Barker, Macleod and Alexander on the excitatory process observed in the exposed human heart stimulated greater effort to obtain more exact knowledge of conduction disturbances

In 1931 Wilson, Macleod and Barker³⁴ attempted by analytic methods to show that the view of the aforementioned investigators that so-called right branch block was left branch block and vice versa was not necessarily in conflict with the hypothesis that the electric axis at a given instant points in the average direction in which the excitation process is spreading at the moment "Both the dextrocardiogram and the levocardiogram, canine and human, are dominated by electrical effects produced by the ventricular septum. Preponderant hypertrophy of one ventricle increases the magnitude of the electrical effects produced by the opposite ventricle by increasing the mass of its septal wall without altering its lateral wall."

In 1932 Wilson, Macleod and Barker⁹ showed that the order in which in human beings the two ventricles pass into the excited state in bundle branch block can be determined by means of serial precordial leads. These precordial leads are so taken that relative negativity of the exploring electrode produces an upward deflection. The chief upstroke signals the arrival of the excitation process at the epicardial surface of the subjacent portions of the ventricular wall. In cases of bundle branch block the upstroke is early when the exploring electrode is placed over the contralateral ventricle and late when it is placed over the homolateral ventricle. The time of the chief upstroke is measured with reference to the first ventricular deflection in lead I, which is taken simultaneously with each precordial lead. In cases in which the standard electrocardiograms exhibit all the features regarded characteristic of bundle branch block of the less common variety, the chief upstroke is early with leads from the left side of the precordium and late with leads from the right side. Later, the authors used a modification of their original method to study the electrocardiographic changes produced by high grade intraventricular block which did not display all the characteristics generally considered necessary for the diagnosis of bundle branch block. Their first study³⁵ (1934) was concerned with an attempt to locate the conduction defect responsible for curves of the standard electrocardiogram with a QRS interval measuring 0.12 second or more, a narrow R deflection and a broad S deflection in lead I, a narrow Q or S deflection synchronous with R in lead I, and a

34 Wilson, F. N., Macleod, A. G., and Barker, P. S. The Interpretation of the Initial Deflections of the Ventricular Complex of the Electrocardiogram, *Am Heart J* 6: 637, 1931.

35 Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S. Electrocardiograms That Represent the Potential Variations of a Single Electrode, *Am Heart J* 9: 447, 1934.

broad upward deflection synchronous with S in the same lead. This curve ordinarily might be considered as indicative of bundle branch block of the rare type. The precordial leads from the right side of the precordium showed a late chief upstroke, while those from the left side showed an early chief upstroke, approximately synchronous with the peak of R in lead I. The curves were strikingly similar to those obtained by the same method of leading after section of the right branch of the bundle of His in dogs. They concluded therefore that these not uncommon curves represented right bundle branch block in man.

The same year (1934) Wilson, Johnston and Barker³⁶ studied similarly 3 patients who presented curves of a less common type, in which in lead I all the ventricular deflections were small, with a conspicuous S deflection and a usually flat or upright T wave, while in leads II and III the ventricular deflections were similar in all respects to those seen in cases of bundle branch block of the left, or common, variety. With the precordial lead the ventricular complex was found to be like those for dogs with right branch block and for patients with a diphasic ventricular complex of the rare type. They concluded that these curves represented right bundle branch block and that some additional factor might modify the form of the electrocardiogram. They pointed out that Maham²⁶ had studied histologically a case in which there was a similar electrocardiogram and had found, as the result of an infarct on the anterior and septal wall of the left ventricle, lesions interrupting the right branch and the anterior division of the left branch.³⁷ In figures 63, 72, 89, 95 and 100 of Maham's book the curves also showed a conspicuous S deflection in lead I, quite different from curves usually attributed to left bundle branch block.

Brown³⁸ (1936), from a study of esophageal and precordial leads, concluded that the common type of bundle branch block is the left, that bundle branch block does not necessarily give rise to "opposing T waves" and that right bundle branch block may be present in cases in which there are conventional curves of the common type and therefore likely occurs more often than is usually admitted under the new terminology. Two cases of the common type were probably of a "mixed" or "partial" variety. "Interpretations relying only on the basis of the directions of the main deflections in standard leads I and

36 Wilson, F. N., Johnston, F. D., and Barker, P. S. Electrocardiograms of an Unusual Type in Right Bundle-Branch Block, *Am Heart J* 9 472, 1934.

37 Maham,²⁶ observation VI on page 242.

38 Brown, W. H. A Study of the Esophageal Lead in Clinical Electrocardiography. I. The Application of the Esophageal Lead to the Human Subject with Observations on the Ta-Wave, Extrasystoles and Bundle-Branch Block, *Am Heart J* 12 1, 1936.

3 are not always reliable in indicating the site of the responsible lesion in bundle branch block." The curves of ventricular extrasystoles supported the work also of the Wilson school

Graybiel and Sprague,³⁹ in analyzing 395 cases of bundle branch block in 1933, outlined a classification, based purely on types of clinical curves

1 (A) Left bundle branch block—homophasic type, in which the curves fulfil all the criteria of complete left bundle branch block [new terminology] except that the T wave and the QRS complex are similarly directed in lead I (26 cases)

1 (B) Left bundle branch block—heterophasic type, in which the curves fulfil all the classic criteria of complete left bundle branch block (99 cases)

2 Right bundle branch block—heterophasic type, in which the curves fulfil all the classic criteria of right bundle branch block (there was no instance of the homophasic type in the 29 cases)

3 Bundle branch block—indeterminate type, in which the T wave is often but not always oppositely directed to the QRS complex and the QRS complex is often similarly directed in leads I and III (81 cases)

4 Significant aberration of the ventricular complex (probably indicating slight degrees of intraventricular bundle branch block), in which the QRS wave is usually slurred and notched but its duration is slightly if at all prolonged and in which the direction of the T wave is variable (160 cases)

These authors excluded cases of marked axis deviation, which often gives curves resembling bundle branch block, and cases of so-called functional bundle branch block

Bayley⁴⁰ (1934), following Wilson's school, classified the curves obtained in 70 cases of right bundle branch block as follows

Group 1 These curves are obtained in cases of bundle branch block of the less common type, corresponding to group II of Graybiel and Sprague (14 cases)

Group 2 These curves are similar to those of group 1 except that in lead I the amplitude of the R spike is greater than that of the S deflection (23 cases)

Group 3 These curves show in lead I a ventricular complex similar in all respects to that in group 2, but in lead III the most conspicuous QRS deflection is a slender deep inverted spike, usually preceded by a small summit and invariably followed by a broad summit, the amplitude of this last deflection being less than that of the inverted spike (28 cases)

Group 4 In lead III of these curves the initial deflection is a small summit, which is followed, as in the curves in group 3, by a deep inverted spike. At its apex the inverted spike is narrow, but the ascending limb, after rising sharply, usually shows a pronounced notch, beyond which its ascent is gradual. The base of the inverted spike is therefore greatly broadened. In some instances this broad upward movement in lead III is absent, and the ascending limb returns quickly to the base line and does not leave it during the remainder of the QRS interval

39 Graybiel, A., and Sprague, H. B. Bundle Branch Block. An Analysis of Three Hundred and Ninety-Five Cases, *Am J M Sc* **185** 395, 1933

40 Bayley, R. H. The Frequency and Significance of Right Bundle-Branch Block, *Am J M Sc* **188** 236, 1934

The distinguishing feature of these curves is the absence of a broad upstroke at the end of the QRS interval in lead III. In lead I the QRS deflection is similar to that of groups 2 and 3, except that R is usually taller and broader and S less conspicuous. T is usually upright. Some of the curves of groups 3 and 4 might easily be confused with those that represent left bundle branch block, from which they may be differentiated by the presence of a conspicuous and broad S in lead I.

In Bayley's series there were only 103 cases of left bundle branch block, as compared with these 70 designated as representing right bundle branch block, a ratio indicating that right bundle branch block is far more common than had been supposed.

Edeiken and Wolferth⁴¹ called attention, in 1934, to the clinical significance of the M-shaped or W-shaped QRS complex in lead II of the electrocardiogram, which they said is due probably to an abnormality of intraventricular conduction as a result of myocardial disease. The amplitude of the QRS complex in lead II does not exceed 5 mm. All the components of the complex are above the base line in the M-shaped complex and below the base line in the W-shaped complex. Occasionally there is a deflection either preceding or following the M-shaped or W-shaped part of the complex, opposite in direction to its associated M-shaped or W-shaped component. The duration of the M-shaped or the W-shaped part is at least 0.08 second.

Von Deesten and Dolganos,⁴² in 1934, described a form of atypical bundle branch block with a favorable prognosis, characterized by (1) a prolonged QRS complex, (2) an R wave in lead I of moderate amplitude and short duration followed by a prolonged notched S wave of smaller amplitude, (3) an upright T wave in leads I and II, (4) a downward directed initial phase of the QRS complex in lead III, returning quickly to above the iso-electric line, where the curve is notched and prolonged, with the T wave in lead III directed downward, and (5) a QRS complex in lead II similar in most instances to that in lead I except for a lower amplitude. They stated that the localization of the lesion causing these curves is uncertain.

Wolferth and Wood⁴³ (1933) and later Roberts and Abramson⁴⁴ (1936) discussed electrocardiographic curves with a ventricular com-

41 Edeiken, J., and Wolferth, C. C. Clinical Significance of the M- or W-Shaped QRS Complex in Lead II of the Electrocardiogram, *Am J M Sc* **188** 842, 1934.

42 von Deesten, H. T., and Dolganos, M. Atypical Bundle-Branch Block with a Favorable Prognosis, *Am J M Sc* **188** 231, 1934.

43 Wolferth, C. C., and Wood, F. C. The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts. Hypothesis of an Accessory Pathway of Auriculoventricular Conduction (Bundle of Kent), *Am Heart J* **8** 297, 1933.

44 Roberts, G. H., and Abramson, D. I. Ventricular Complexes of the Bundle-Branch Block Type Associated with Short P-R Intervals, *Ann Int Med* **9** 983, 1936.

plex typical of the bundle branch block associated with a short PR interval, similar to the curves in cases previously described by Wilson ⁴⁵, Wedd ⁴⁶, Hamburger ⁴⁷, Pezzi ⁴⁸, Wolff, Parkinson and White, ⁴⁹ and Holzmann and Scherf ⁵⁰. In some instances factors producing inhibition of vagal influences or the administration of quinidine brought about a transition to normal. One theory for this mechanism is that an accessory pathway of auriculoventricular conduction, such as that described by Kent ⁵¹ between the right auricle and the right ventricle, might exist in these cases and permit an actual acceleration of the passage of the impulse from the auricle to a section of the ventricle.

REVIEW OF CLINICAL STUDIES OF PERMANENT BUNDLE BRANCH BLOCK ⁵²

A number of studies of series of clinical cases of bundle branch block have been made since 1912. In that year Mathewson ²⁸ reported 4 cases, 3 of left bundle branch block and 1 of right bundle branch block. In the last case the impairment of conduction was functional rather than permanent, since the form of the curve changed in the same electrocardiogram. Carter's ⁵ report in 1914 included 22 cases and indicated the frequency of left bundle branch block as compared with that of right bundle branch block, of which there was only 1 case in the series. There was a large incidence of aortic valvular disease, and the serious prognosis regarding the conduction defect was suggested. Carter pointed out the frequent association of impaired auriculoventricular conduction, stating that the junctional tissues as a whole have special pathologic propensities. The cases fulfilled the rigid cri-

45 Wilson, F. N. A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, *Arch Int Med* **16** 1008 (Dec) 1915

46 Wedd, A. M. Paroxysmal Tachycardia, *Arch Int Med* **27** 571 (May) 1921

47 Hamburger, W. W. Bundle-Branch Block, *M Clin North America* **13** 343, 1929

48 Pezzi, C. Considerations pathogeniques sur quelques cas de rythme septal et paraseptal permanents, *Arch d mal du cœur* **24** 1, 1931

49 Wolff, L., Parkinson, J., and White, P. D. Bundle-Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *Am Heart J* **5** 685, 1930

50 Holzmann, M., and Scherf, D. Ueber Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, *Ztschr f klin Med* **121** 404, 1932

51 Kent, A. F. S. Observations on the Auriculo-Ventricular Junction of the Mammalian Heart, *Quart J Exper Physiol* **7** 193, 1914

• 52 The new terminology of bundle branch block is used throughout this article, even when the author quoted used the old terminology

teria he established but which in 1918 he⁵³ modified somewhat to include cases in which there was low voltage as indicating involvement of both branches or their arborizations. In bringing forth their concept of "arborization block," in 1917, Oppenheimer and Rothschild²⁹ reported a series of 14 cases, with necropsies, showing that the curves described usually indicated extensive chronic degenerative changes of the myocardium associated with a serious prognosis. Willius³⁰ (1919) collected reports of 138 similar cases, in 69.6 per cent of which death occurred within an average of eight and a half months. In this series chronic endocarditis was diagnosed in 35.5 per cent of the cases and exophthalmic goiter in 5 cases, the remainder of the conditions belonging to the so-called degenerative group.

Herrick and Smith⁵⁴ (1922) published a study of 35 cases of bundle branch block, of which 32 fulfilled criteria of left branch interruption. Only 6 patients were under 50 years of age. All the patients had symptoms and physical signs of cardiac weakness (severe in 17). Only 1 patient had definite chronic valvular disease, although 10 had had rheumatic fever. Eleven patients died within eighteen months. In 1 case the QRS complex changed from moderate amplitude with large notching to large amplitude with slight notching as the congestive failure advanced, and changes from typical bundle branch block to a more normal complex occurred as the patient improved. Six patients had impaired auriculoventricular conduction, and 5 had auricular fibrillation.

White and Viko⁵⁵ (1923) found records of 130 cases of intraventricular block among 3,219 cases in which electrocardiograms were made. In 41 cases there was the so-called complete type of bundle branch block, in the others there was aberration of the ventricular complex. The "complete" type was shown by 34 males and 7 females, and only 2 were under 40 years of age, the average age being 60 years. In 40 cases there was left bundle branch block. The etiologic factor was thought to be arteriosclerosis in 33 cases, rheumatic fever in 4 cases and syphilis in 3 cases. Angina pectoris occurred in 8 cases and congestive failure in 23. Hypertension was found in 24 cases. In 14 cases auriculoventricular block also was present, being complete in 2. Auricular fibrillation coexisted in 7 cases. Thirteen of the patients died of heart failure within one year. The data relating to the cases

53 Carter, E. P. Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations, *Arch Int Med* **22** 331 (Sept.) 1918.

54 Herrick, J. B., and Smith, F. M. Clinical Observations on a Block of the Branches of the Auriculoventricular Bundle, *Am J M Sc* **164** 469, 1922.

55 White, P. D., and Viko, L. E. Clinical Observations on Heart Block, *Am J M Sc* **165** 659, 1923.

in which there were lesser degrees of intraventricular block were strikingly similar. In this group of 89 cases there existed also auriculoventricular block in 20 (complete in 12) and auricular fibrillation in 15. These authors also found among the 3,219 patients 156 cases of auriculoventricular block, of which 27 were complete and 129 incomplete. In 15 of the cases of complete heart block there was evidence of intraventricular block, 3 with well marked bundle branch block, and in 19 of the cases of partial block there was intraventricular block also. The incidence of heart failure was greater in the cases of intraventricular block than in those of auriculoventricular block, especially heart failure of the anginal type. Angina pectoris was found about four times more often in cases of intraventricular block.

Hart⁵⁶ (1925), also using Carter's criteria, reported on 25 cases, in 23 of which there was left bundle branch block. All but 5 patients were under 50 years of age, and 16 died within a few months. All had advanced heart disease. There were 16 males and 9 females.

Talley and Reed⁵⁷ (1926) studied 28 cases. Only 1 patient was under 40 years of age, and the diagnosis was chronic myocarditis in 23 cases. Nineteen were males, and 9 were females. There were 20 cases of left, 3 of right, 1 of alternating right and left and 4 of partial right bundle branch block. In 6 cases there was impaired auriculoventricular block also and in 8 auricular fibrillation. Fifteen patients died within six months. Two patients were alive after four and a half years. Congestive failure was the common end.

Willius⁵⁸ (1926) collected reports of 105 cases of "complete" bundle branch block, of which 99 were cases of left bundle branch block. The youngest patient was 17 years old and the oldest 88, but 87 patients were over 50. There were 60 males and 45 females. In 93 per cent of the cases there was hypertensive and arteriosclerotic heart disease, but most of the patients were ambulatory. Angina pectoris was present in 31 cases, but a history of cardiac infarction was obtained in only 1 case. Dyspnea was noted in all cases. Auricular fibrillation existed in 4 cases and a prolonged PR interval in 3. Forty-three of 66 patients were dead of heart failure within fourteen months, 18 were living, 2 as long as six years afterward.

56 Hart, T. S. Block of the Branches of the Bundle of His. Clinical Notes on the Changes Following the Administration of Digitalis, Comments on the Levocardiogram, Dextrocardiogram and Bicardiogram, *Arch Int Med* **35** 115 (Jan.) 1925.

57 Talley, J. E., and Reed, O. K. A Study of Twenty-Eight Cases of Bundle-Branch Block, *Am Heart J* **1** 262, 1926.

58 Willius, F. A. Clinical Features of Cases Exhibiting Electrocardiograms Conforming to Those of Experimental Complete Bundle-Branch Block, *Am Heart J* **1** 576, 1926.

In Cowan and Bramwell's⁵⁹ (1925) series of 24 cases 23 were so-called typical cases of left bundle branch block. All but 3 patients were over 40 years old, and there were 20 males and 4 females. The principal complaint was dyspnea in 13 cases and anginal pain in 8. Cardiac enlargement was present in 14. There were 10 cases of chronic valvular disease and 2 of congenital heart disease, and in the others there was evidence of arterial degeneration. The blood pressure was over 150 systolic in 10. Auricular fibrillation was present in 5 cases and auriculoventricular block in 1. In the latter case the patient first showed complete heart block without bundle branch block, and three months later the two arrhythmias combined. Another patient had at first only an inverted T wave in leads I and II and one year later had left bundle branch block after a sudden cardiac attack. One patient showed bundle branch block which after five months was much less pronounced. Fourteen patients had died, all within eighteen months and 11 within a year. Only 1 had been under observation for as long as four years.

Of Bach's⁶⁰ 80 patients (1930) 50 had degenerative heart disease, 17 had syphilitic heart disease and 11 had mitral stenosis. For those with degenerative heart disease the average age was 59 years, and 20 per cent of the patients died within a year. However, 1 patient was living after fourteen years, 1 after nine years and 23 after seven years. Nine of the syphilitic patients died at the average age of 45 years, whereas only 1 of the rheumatic patients was dead. Some patients, especially those with degenerative heart disease, showed a low voltage, with left axis deviation at first and later slight lengthening and notching of the QRS complex, and finally left bundle branch block.

Luten and Grove⁶¹ (1929) presented a study of 237 cases which did not fulfil the commonly accepted criteria of bundle branch block but which the authors considered as instances of defective conduction in the right branch but which possibly they might now change to that of the left branch. The QRS complex was upright in lead I and the T wave inverted, whereas the QRS complex was downward in lead III and the T wave was upright, but the QRS interval was less than 0.1 second. The number of these cases in which a diagnosis of cardiac disease was given as the principal or secondary consideration amounted

⁵⁹ Cowan, J., and Bramwell, J. C. Clinical Aspect of Bundle-Branch Block, *Quart J Med* **19** 95, 1925.

⁶⁰ Bach, F. On the Clinical Significance of Right Bundle Branch Block, *Quart J Med* **23** 261, 1930.

⁶¹ Luten, D., and Grove, E. The Incidence and Significance of Electrocardiograms Showing the Features of Left Axis Deviation and QRS of Normal Duration with Inverted T₁ and Upright T₃, *Am Heart J* **4** 431, 1929.

to only 56 per cent of the total number. Only 11 patients were under 35 years of age. Hypertension was present in 89 per cent of all cases and arteriosclerosis in 78 per cent. In 100 of the 132 cases of cardiac disease there was evidence of coronary arteriosclerosis, hypertensive heart disease or angina pectoris. There were 25 cases of syphilitic heart disease or aneurysm, 5 of rheumatic heart disease, 1 of "thyroid heart disease" and 1 of bacterial endocarditis. In only 6 of the remaining 102 cases was there neither arteriosclerosis nor hypertension. Cardiac hypertrophy was present in 110 cases (48 per cent) and probably in 97 others. Seven necropsies had been performed, and in all cases there was significant coronary arteriosclerosis.

In 39 of the 41 cases of classic bundle branch block studied by Hill⁶² (1930) there was block of the left branch. All but 2 of the patients were over 40 years old, and there were 31 males and 10 females. All the patients had dyspnea, 15 had angina pectoris and 12 had edema. Hypertension was present in 15 cases, and aortic regurgitation in 4, and there was a rheumatic history in 3. Chronic valvulitis was present in some cases and toxic goiter in a few. The patients all died within a year or a little more. Auricular fibrillation occurred in 10 cases and auriculoventricular block in 5, with an increased PR interval in several others. Faint heart sounds and an apical systolic murmur were common.

Campbell and Turkington⁶³ published a study, in 1931, of 56 cases of left bundle branch block (they used the old terminology—right bundle branch block). All but 9 patients were over 40 years of age, and the average age was 58.6 years for hospitalized patients and 63.1 years for private patients. There were 36 males and 20 females. The cardiac diagnoses were not clearly stated, but there was a history of previous rheumatic infection in 9 cases, syphilis in 3 cases, bacterial endocarditis in 2 cases and definite peripheral arteriosclerosis in 14 cases. The blood pressure was over 150 systolic in 26 cases and over 200 systolic in 3 cases. Evidence of disease of the mitral valve was present in 34 cases and disease of the aortic valve in 8 cases. Dyspnea was noted in 43 cases, anginal pain in 22 cases, marked heart failure in 34 cases, edema in 15 cases and cardiac enlargement in almost all cases, being severe in 10 cases. Auricular fibrillation was noted in 4 cases. Thirty patients died within six years. Of the 22 patients known to be living, 4 were alive after nine years, 1 after thirteen years and another after seven years. The remainder lived less than three years.

62 Hill, I. G. H. Bundle-Branch Block. A Clinical and Histological Study, *Quart J Med* **24** 15, 1930-1931.

63 Campbell, S. B. B., and Turkington, S. I. Right Bundle-Branch Block. An Analysis of the Clinical Records of Fifty-Six Cases with Typical Electrocardiograms, *Quart J Med* **24** 481, 1931.

Smith's⁶⁴ (1932) 47 patients were all ambulatory when first seen. The youngest patient was 36 years old. There were 34 males and 13 females. All but 3 were dead after eighteen months. These 3 were living after three, four and five years, respectively.

The report of Tung and Cheer⁶⁵ (1933) from China was interesting because in 10 of the 16 cases there was right bundle branch block. One patient was 10 years old, another 11 and the others 28 or over. There were 11 males and 5 females. Seven of the patients with right bundle branch block had rheumatic heart disease with mitral stenosis, 2 had coronary arteriosclerosis and 1 had congenital dextrocardia, with evidence of a patent septum. Of the patients with left bundle branch block, 5 had hypertension and 1 arteriosclerotic heart disease. Three patients with mitral stenosis first had preponderance of the right ventricle and later right bundle branch block. The authors suggested that many cases of ventricular preponderance are probably due, in part at least, to defective bundle branch conduction. They said they believed that dilatation and stress and strain of a ventricle are factors in producing intraventricular block.

Graybiel and Sprague³⁹ reported (1933) on a great series of 395 cases as an extension of the report of White and Viko⁵⁵ (1923). They classified their cases according to the types of curves, as already shown. There were 26 cases of left bundle branch block of homophasic type, 99 cases of left bundle branch block of heterophasic type, 29 cases of left bundle branch block of heterophasic type, 81 cases of right bundle branch block of heterophasic type, 160 cases of bundle branch block of indeterminate type and 109 cases in which there was found to be significant aberration of the ventricular complex. All but 45 patients were over 40 years of age, and 216 were between 40 and 70. There were 301 males and 94 females. Probable coronary arteriosclerosis was present in 238 cases, hypertension in 154, rheumatism in 47 and chronic pericarditis in 11. The heart was enlarged in 154 of 166 cases, mitral stenosis was present in 35 cases, mitral regurgitation in 36, aortic stenosis in 11 and aortic regurgitation in 49. There was evidence of definite coronary occlusion in 31 cases and of aortic aneurysm in 2. Auricular fibrillation existed in 54 cases, partial heart block in 20 and complete heart block in 17. Congestive failure occurred in 118 cases, angina pectoris in 59, Adams-Stokes attacks in 12, cardiac asthma in 12 and effort syndrome in 4. Of 308 patients followed, 85 were living.

64 Smith, A. L. Review of Forty-Seven Cases of One-Sided Branch Block, *Nebraska M. J.* **17** 179, 1932.

65 Tung, C. L., and Cheer, S. N. A Correlation of Clinical and Electrocardiographic Findings in Human Bundle-Branch Block, *Chinese M. J.* **47** 15, 1933.

an average of two years and eleven months later, whereas 223 died within an average of fourteen months

King ⁶⁶ (1934) analyzed 155 instances of bundle branch block in 150 patients. There were 134 instances of left and 21 of right bundle branch block, although in 5 cases the block changed from one side to the other. The average age of the patients with "senile" heart disease was 61 years, of those with syphilitic heart disease 42 years and of those with rheumatic heart disease 42 years. There were 109 males and 41 females. The etiologic agents held responsible were arteriosclerosis (coronary) in 108, syphilis (aortic) in 14 and rheumatic fever (causing valvulitis) in 15, with a doubtful etiologic agent in 18. Auricular fibrillation occurred in 26 cases (22 cases of left and 4 cases of right branch block). Prolongation of the PR interval was observed in 28 cases and complete heart block in 36. The author showed that bundle branch block may be expected to occur in about 2 per cent of all patients suffering from syphilitic cardiovascular disease and in 5.5 per cent of all patients with rheumatic infection of various types. Of 104 patients traced, 76 were dead, the average duration of life after the diagnosis of bundle branch block was made being one year for the senile patients, ten and six-tenths months for the syphilitic patients and one year and eight months for the rheumatic patients. There were autopsies in 17 cases with a close correlation between the clinical and the gross pathologic diagnosis.

Mention has previously been made of an "atypical bundle-branch block with a favorable prognosis" described by von Deesten and Dolganos ⁴² (1934). One patient was living after eleven and a half years, at the age of 72 years, and another after eight and a half years, at the age of 54 years.

Mention has also been made of the article by Edeiken and Wolferth ⁴¹ (1934) concerning cases in which there was an M-shaped or W-shaped QRS complex in lead II, which is apparently a manifestation of arteriosclerotic heart disease and often results from coronary occlusion.

Bayley ⁴⁰ (1934) discussed the frequency and significance of right bundle branch block as observed at Ann Arbor, Mich. There were 70 cases, as compared with 103 cases of left bundle branch block, a much higher incidence than in any of the previous reviews by other authors. Bayley divided the cases of right branch block into four groups, which have already been described. He stated that the position of the heart, infarction in the septum or free wall of the left ventricle and preponderance of the left ventricle are probably the chief factors, absence or

⁶⁶ King, J. T. Bundle-Branch Block. A Case Analysis with Especial Reference to Incidence and Prognosis, *Am J M Sc* **187** 149, 1934.

presence of which, singly or in combination, accounts for the variation in form of the initial deflection in curves for patients with complete right bundle branch block. He found both right and left branch block to be considerably more common with arteriosclerotic heart disease than with other etiologic types. Often little or no evidence of cardiovascular disease was found on routine physical examination. "When patients with rheumatic heart and mitral stenosis develop bundle-branch block, the conduction defect is almost invariably on the right side."

Wood, Jeffers and Wolferth⁶⁷ (1935) reported a follow-up study of 64 patients with a defect of right bundle branch conduction. Because a large number of these patients had lived several years, the authors concluded that in the absence of other evidence of heart disease, bundle branch block is not necessarily an ominous sign. Three fourths of the patients were over 50 years of age when first seen. In 3 patients the block developed during observation, the first had practically no evidence of cardiovascular disease, the second had definite disease of the coronary artery and the third showed the deformity during a fatal attack of coronary occlusion. In 3 cases the QRS deformity appeared and disappeared from time to time. Twenty patients showed no evidence of heart disease when first seen, 13 showed relatively minor evidence and 17 showed definite evidence of heart disease.

Salcedo-Salgar and White⁶⁸ (1935) became interested in the relation of all forms of conduction block to clinical manifestations of disease of the coronary arteries. Only 8.8 per cent of 700 patients with angina pectoris showed heart block, either auriculoventricular (1.1 per cent) or intraventricular (7.3 per cent) or both (0.4 per cent), and only 13.1 per cent of 328 patients with coronary thrombosis showed heart block, either auriculoventricular (3.6 per cent) or intraventricular block (8.9 per cent) or both (0.6 per cent). Of 181 patients with intraventricular block of all grades, 29.8 per cent showed angina pectoris without clinical coronary thrombosis, and only 9.3 per cent showed coronary thrombosis, making a grand total of 46.9 per cent of the patients with intraventricular block with clear evidence of disease of the coronary arteries, as compared with 21.3 per cent of the patients with auriculoventricular block with the same evidence. A few over half of those with typical left bundle branch block and the same number of those with typical right bundle branch block had angina pectoris or coronary thrombosis or both. The prognosis for patients over 50 years

67 Wood, F. C., Jeffers, W. A., and Wolferth, C. C. Follow-Up Study of Sixty-Four Patients with a Right Bundle-Branch Conduction Defect, *Am Heart J* **10** 1056, 1935.

68 Salcedo-Salgar, J., and White, P. D. The Relationship of Heart-Block, Auriculoventricular and Intraventricular, to Clinical Manifestations of Coronary Disease, Angina Pectoris, and Coronary Thrombosis, *Am Heart J* **10** 1067, 1935.

of age with either auriculoventricular or intraventricular block was about equally unfavorable whether or not there were associated clinical evidences of disease of the coronary arteries

Sampson and Nagle⁶⁹ (1936) discussed the prognosis of bundle branch block as determined by a study of 157 cases conforming to Carter's criteria and the prognosis for a group of 112 heterogeneous examples of atypical block of the intraventricular conduction system. There were 146 cases of classic left bundle branch block and 11 cases of classic right branch block. The authors noted a high fatality during the first year after discovery of classic bundle branch block and a remarkable diminution of the fatality rate for patients who survived this period, some patients living as long as eleven years. The patients with atypical intraventricular block had about the same life expectancy after they reached the later decades, and some lived as long as sixteen years. Among the 157 patients with classic branch block there were 96 males and 61 females; among the 112 patients with intraventricular block there were 75 males and 37 females. All but 14 of the patients with classic block were 40 or more years of age, and all but 28 of those with atypical block were 40 or more years of age. Arteriosclerotic heart disease and arteriosclerotic combined with hypertensive heart disease comprised the etiologic factors in 108 of the cases of classic block and 58 of the cases of atypical block; approximately two thirds of each group. There were a total of 23 cases of syphilitic heart disease, 22 cases of rheumatic heart disease, 11 cases of thyrotoxic heart disease, 7 cases of congenital heart disease and 40 cases in which there were miscellaneous or doubtful etiologic factors.

As regards prognosis, Bishop and Bishop⁷⁰ (1932) suggested caution, since a patient with hypertensive heart disease with "complete" left bundle branch block was observed by them for eleven years and was well at the time of the report.

As a rare cause of right bundle branch block Crawford and de Veer⁷¹ (1932) described an aneurysm, 9 cm in diameter, arising in the first portion of the aorta which produced marked stenosis of the pulmonary valve and projected into the right ventricle, with considerable damage to the interventricular septum. Serial sections, studied by Alfred E. Cohn, were not satisfactory. The authors referred to a similar case reported by Rothschild, Sacks and Libman, in 1927, and another reported

69 Sampson, J. J., and Nagle, O. E. The Prognosis of Bundle-Branch Block and Other Intraventricular Conduction System Lesions, *Am J M Sc* **191** 88, 1936

70 Bishop, L. F., and Bishop, L. F., Jr. Bundle Branch Block of Unusual Duration, *J A M A* **98** 398 (Jan 30) 1932

71 Crawford, J. H., and de Veer, J. A. Aneurysm of the Aorta Producing Pulmonary Stenosis and Bundle-Branch Block, *Am Heart J* **7** 780, 1932

by Stejfa, in 1930. In the latter case the diagnosis of this unusual lesion was made ante mortem on the basis of a rough systolic murmur in the second and third left interspaces, with enlargement of the heart to the right and to the left and signs of aortic insufficiency accompanied with tracheal tug and paralysis of the left recurrent laryngeal nerve. The description of the study of the bundle branches was vague.

TRANSIENT, INTERMITTENT AND "FUNCTIONAL" BUNDLE BRANCH BLOCK

For many years it has been recognized that bundle branch block is not always a permanent phenomenon. Probably if electrocardiograms were made more often, the transient or intermittent nature of the block would be evident more frequently.

Transient or intermittent bundle branch block may occur without evidence of organic heart disease, in which event it is more likely to be designated functional bundle branch block. Such cases are rare, however, since in most instances there are definite indications of cardiac disease and the occurrence of bundle branch block even transiently is presumptive evidence of the presence of organic heart disease.

One form of intermittent and recurrent bundle branch block is assumed to be of purely functional origin and not dependent on heart disease. This is the syndrome of bundle branch block with a short PR interval in healthy young persons prone to paroxysmal tachycardia or auricular fibrillation. It was first described, in 1930, by Wolff, Parkinson and White,⁴⁵ although Wedd,⁴⁶ in 1921, reported a case of the same nature which he assumed, however, to be due to an auriculoventricular nodal rhythm. In such cases the reversion to a normal ventricular complex, with a longer (normal) PR interval, spontaneously or by vagal release after exercise or atropinization is often but not always a striking phenomenon. While this feature was present in some of the cases reported by Wolff, Parkinson and White and in the 2 reported by Tung⁷² (1936), it did not exist in the cases reported by Holzmänn and Scherf⁵⁰ (1932), Wolferth and Wood⁴⁸ (1933) and Roberts and Abramson⁴⁴ (1936). In the case reported by Roberts and Abramson the use of quinidine was followed by the appearance of a normal electrocardiogram. Also, at times there was spontaneous transition from the abnormal complex alone to alternate grouping of abnormal and normal complexes. Holzmänn and Scherf and later Wolferth and Wood postulated the presence of a band of aberrant conduction tissue between the right auricle and the right ventricle and stated that the conduction wave passes not only through the bundle of His and its branches but also over this aberrant bundle. Reaching the right ventricle via the

⁷² Tung, C. Functional Bundle-Branch Block, *Am Heart J* **11** 89, 1936

usual route, the wave finds the ventricle already activated by the impulse which has passed down the aberrant bundle and therefore refractory. Although Kent⁵¹ (1914) described such an aberrant bundle in animals, no one has yet demonstrated it in the heart of man.

Palmer and White⁷³ (1928) found 107 cases of aberrant ventricular response to an auricular premature beat (with a normal response to normal auricular stimuli) in 387 consecutive cases in which the electrocardiogram showed an auricular premature beat. Such an abnormal ventricular response is assumed to be due to temporary fatigue of one branch of the bundle of His. These aberrant complexes had been described previously by others (Lewis,⁷⁴ 1909 and 1911, Robinson,⁷⁵ 1915, White and Stevens,⁷⁶ 1916, Levy,⁷⁷ 1922, Stenstrom,⁷⁸ 1924).

Mentzingen⁷⁹ (1934) reported an unusual case, that of a woman aged 54 years who had vasomotor spasms of the hands. An electrocardiogram showed left bundle branch block, which disappeared when amyl nitrite was administered. The effect wore off in several minutes, with sudden shifts from complexes typifying bundle branch block to normal complexes, without changes in the PR interval or in the heart rate and without transitional forms.

An interesting association of intermittent bundle branch block (left) with pneumonia and hyperthyroidism due to exophthalmic goiter was reported by Lamb⁸⁰ (1933) in the case of a woman aged 27 years. The block was assumed to be due to the toxic effect of infection plus tachycardia. The aberrant complexes recurred, with subsequent exacerbations of the hyperthyroidism. At times the aberrant complexes were interspersed with normal complexes.

Lewis⁷⁴ (1909, 1 case, 1911, 2 cases) was apparently the first to describe transient bundle branch block in cases of organic heart disease.

73 Palmer, R. S., and White, P. D. The Clinical Significance of Aberrant Ventricular Response to Auricular Premature Beats and to Paroxysmal Auricular Tachycardia, *Am Heart J* **4** 153, 1928.

74 Lewis, T. (a) Paroxysmal Tachycardia, the Result of Ectopic Impulse Formation, *Heart* **1** 262, 1909-1910, (b) footnote 27.

75 Robinson, G. C. The Action of the Vagus on the Heart in Paroxysmal Tachycardia, *Arch Int Med* **16** 967 (Dec.) 1915.

76 White, P. D., and Stevens, H. W. Ventricular Response to Auricular Premature Beats and to Auricular Flutter, *Arch Int Med* **18** 712 (Nov.) 1916.

77 Levy, R. L. Clinical Studies of Quinidin, *Arch Int Med* **30** 451 (Oct.) 1922.

78 Stenstrom, N. An Experimental and Clinical Study of Incomplete Bundle-Branch Block, *Acta med Scandinav* **60** 552, 1924.

79 von Mentzingen, A. Ueber einen Fall von funktionellem Verzweigungsblock, *Klin Wchnschr* **13** 1158, 1934.

80 Lamb, A. E. Bundle-Branch Block in Hyperthyroidism, *M Times & Long Island M J* **61** 234, 1933.

Since then many similar cases have been reported. The following list includes the names of most of the authors of such publications: Mathewson²⁸ (1912, 1 case in which both conduction methods were displayed in the same record), Carter⁵ (1914, 1 case), Wilson⁴⁵ (1915, 1 case, showing four different rhythms and three different ventricular complexes produced by stimulation of the vagus nerve and abolished in favor of the normal rhythm by the administration of atropine), Robinson⁸¹ (1916, 7 cases of temporary aberration of the ventricular complex following impairment of the functional state of the heart), Danielopolu and Danulescu⁸² (1921, 1 case in which ocular compression with or without atropine or epinephrine was said to cause bradycardia, auriculoventricular block and an atypical QRS complex), Danielopolu and Danulescu⁸³ (1922, 1 case in which strong binocular compression with or without atropinization caused curves typical of bundle branch block to appear), Stenstrom⁷⁸ (1924, 3 cases of temporary failure of intra-ventricular conduction and 5 cases in which there was a single aberrant complex of supraventricular origin), Stenstrom⁸⁴ (1927, 3 cases of bundle branch block in which the block disappeared for periods spontaneously or with slowing of the heart rate by rest or vagal pressure), Lembach and White⁸⁵ (1928, 1 case in which at first there was two to one right bundle branch block and later complete branch block), Samet⁸⁶ (1927, 1 case of intermittent auriculoventricular block, with normal duration of QRS and prolongation of QRS during sinus rhythm), Willhus and Keith⁸⁷ (1927, 3 cases of intermittent incomplete bundle branch block), Wenckebach and Winterberg⁸⁸ (1927, 1 case of bundle branch block, with a prolonged PR interval, in which

81 Robinson, G. C. The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, *Arch Int Med* **18** 830 (Dec) 1916

82 Danielopolu, D., and Danulescu, V. Lésions latentes des branches du faisceau auriculo-ventriculaire, moyens de les décélérer, *Arch d mal du cœur* **14** 529, 1921

83 Danielopolu, D., and Danulescu, V. Trouble de conductibilité dans les branches du faisceau auriculo-ventriculaire provoque chez l'homme normal par l'excitation du vague, *Arch d mal du cœur* **15** 361, 1922

84 Stenstrom, N. Further Experience on Incomplete Bundle-Branch Block in Man, *Acta med Scandinav* **67** 353, 1927

85 Lembach, R. F., and White, P. D. Two to One Right Bundle-Branch Block, *Am Heart J* **3** 422, 1928

86 Samet, B. Zur Kenntnis der intra-ventrikulären Leitungsstörungen, *Wien Arch f inn Med* **14** 15, 1927

87 Willhus, F. A., and Keith, N. M. Intermittent Incomplete Bundle-Branch Block, *Am Heart J* **2** 255, 1927

88 Wenckebach, K. F., and Winterberg, H. Die unregelmässige Herztaetigkeit, Leipzig, Wilhelm Engelmann, 1927

slight exercise produced two to one auriculoventricular block and a normal intraventricular conduction time), von Kapff⁸⁹ (1928, 1 case of transient bundle branch block), Barnes and Yater⁹⁰ (1929, 1 case of paroxysmal tachycardia and alternating incomplete right and left bundle branch block, with fibrosis of the myocardium in a young woman), Moore and Stewart⁹¹ (1930, 1 case of right bundle branch block in a patient with uremia, the block disappeared after the intravenous injection of hypertonic dextrose solution), Slater⁹² (1930, 1 case of three to one and four to one partial bundle branch block, which the author said was an instance of type 2 bundle branch block), Baker⁹³ (1930, 1 case of temporary bundle branch block occurring during tachycardia, with restoration of normal intraventricular conduction as the heart rate became slower or during the administration of oxygen), Kelly⁹⁴ (1930, 1 case of two to one right bundle branch block, which later became complete), Herrmann and Ashman⁹⁵ (1931, 3 cases in which there was sudden transition from complete bundle branch block to normal intraventricular conduction after the taking of a deep breath and the holding of it for from a few seconds to a minute [type 2] and 5 cases of high grades of partial bundle branch block in which with or without other mechanism or disturbances of rhythm there appeared at times a normal short QRS interval), Carter and McEachern⁹⁶ (1931, 1 case in which there were paroxysms of auriculoventricular block, with variable and incomplete bundle branch block but with complete bundle branch block during the phases of sinus rhythm), Katz, Hamburger

89 von Kapff, D W Ueber einen Fall von Passageren Schenkel-Block, *Klin Wchnschr* 7 357, 1928

90 Barnes, A R, and Yater, W M Paroxysmal Tachycardia and Alternating Incomplete Right and Left Bundle-Branch Block with Fibrosis of the Myocardium, *M Clin North America* 12 1603, 1929

91 Moore, N S, and Stewart, H J The Disappearance of Intraventricular Heart Block Occurring in Uremia Following the Intravenous Injection of Hypertonic Glucose Solution, *Am Heart J* 5 469, 1930

92 Slater, S R Partial Bundle-Branch Block A Case of Three-to-One and Four-to-One Block, *Am Heart J* 5 617, 1930

93 Baker, B M, Jr The Effect of Cardiac Rate and the Inhalation of Oxygen on Transient Bundle Branch Block, *Arch Int Med* 45 814 (May) 1930

94 Kelly, L W Two-to-One Right Bundle-Branch Block, *Am Heart J* 6 285, 1930

95 Herrmann, G, and Ashman, R Partial Bundle-Branch Block A Theoretical Consideration of Transient Normal Intraventricular Conduction in the Presence of Apparently Complete Bundle-Branch Block, *Am Heart J* 6 375, 1931

96 Carter, E P, and McEachern, D Recurrent Complete Heart-Block Report of a Case Associated with Transient Bundle-Branch Block and Normal Conduction Between Attacks, *Bull Johns Hopkins Hosp* 49 337, 1931

and Rubinfeld⁹⁷ (1932, 1 case in which a changing ventricular rate caused the appearance of transient bundle branch block of one type superimposed on that of the opposite type, with at times an alternation between the two after injection of epinephrine), Elliott and Nuzum⁹⁸ (1932, 1 case of left bundle branch block, with transient and spontaneous two to one auriculoventricular block during which the bundle branch block disappeared, and with later persistence of the bundle branch block except during slowing from vagal pressure [type 2]), Morris and McGuire⁹⁹ (1932, 2 cases of transient complete bundle branch block of acute onset with circulatory failure), Campbell and Suzman¹⁰⁰ (1932, 1 case in which there was gradual disappearance of bundle branch block, probably owing to coronary thrombosis), Sigler¹⁰¹ (1933, 1 case in which stimulation of the left vagus nerve, paradoxically, removed the bundle branch block, and in which an abnormal QRS complex occurred after as long a rest period as 0.56 second, a normal complex being restored by an additional rest of 0.08 second), Pescador and Villanueva¹⁰² (1932, 1 case of "functional" bundle branch block), Carr¹⁰³ (1933, 1 case in which the bundle branch block at first could be terminated by vagal stimulation but which later became permanent), Bagnaresi¹⁰⁴ (1934, 1 case of paroxysmal tachycardia, with polymorphism of the ventricular complex and typical bundle branch block), Willius and Anderson¹⁰⁵ (1934, 1 case of transient recurrent complete bundle branch block), Kurtz¹⁰⁶ (1936, 6 cases of transient bundle branch block, in 2 of which the occurrence of the block was closely

97 Katz, L. N., Hamburger, W. W., and Rubinfeld, S. H. Partial Bundle-Branch Block, *Am Heart J* **7** 753, 1932

98 Elliott, A. H., and Nuzum, F. R. Bundle-Branch Block with Periods of Normal Intraventricular Conduction. Report of an Unusual Case, *Am Heart J* **7** 680, 1932

99 Morris, R. S., and McGuire, J. Transient Complete Bundle-Branch Block, *Am J M Sc* **184** 202, 1932

100 Campbell, M., and Suzman, S. S. Simultaneous Disappearance of Gallop Rhythm and Bundle-Branch Block, *Lancet* **1** 985, 1932

101 Sigler, L. H. Functional Bundle-Branch Block (Partial) Paradoxically Relieved by Vagal Stimulation, *Am J M Sc* **185** 211, 1933

102 Pescador, L., and Villanueva, S. Un caso de pulso alternante por extrasístoles ventriculares derechos, simulando un bloqueo funcional de la rama izquierda del fascículo de His, *Med iberica* **1** 642, 1932

103 Carr, F. B. Functional Bundle Branch Block, *New England J Med* **209** 1101, 1933

104 Bagnaresi, G. Il blocco di branca instabile, *Cuore e circolaz* **18** 65, 1934

105 Willius, F. A., and Anderson, M. J. Transient, Recurrent Complete Bundle-Branch Block, *Am Heart J* **10** 248, 1934

106 Kurtz, C. M. Transient Complete Bundle-Branch Block, *Am Heart J* **11** 212, 1936

associated with periods of myocardial failure, in another case, block was present for a time after coronary occlusion^{106a}

It is probable that in such cases as most of those mentioned there are partial lesions of one or both bundle branches without complete interruption of function except when toxic or metabolic factors further compromise the conduction tissues or when release of vagal tone increases the heart rate. The onset may be abrupt, as when due mainly to a sudden insult, such as infarction, with gradual disappearance of the block, during the latter part of which period there may be frequent transitions or the onset may be gradual, with or without more or less frequent transitions due to progressive involvement of the branch, or the transitions may occur with great frequency, regularly or irregularly, in cases in which the pathologic process may be relatively stationary, in which event the heart rate may be of greatest importance in the production of the transition. Similar factors are at work in cases of auriculoventricular heart block, in which for days, months or years the degree of block may be variable.

SUDDEN ONSET OF PERMANENT BUNDLE BRANCH BLOCK

A few cases have been observed in which permanent bundle branch block was noted to occur suddenly. It is a fortunate chance that affords such an observation. In Perry's¹⁰⁷ case (1934) the exact cause of the sudden change from a normal complex to that of bundle branch block could not be ascertained with certainty but was assumed to be slow coronary thrombosis in a case in which the bundle branch was already compromised. Another case, 1 of the cases reported by Hollingsworth¹⁰⁸ (1937), was that of a man whose electrocardiographic curve suddenly changed to that typical of bundle branch block while the electrocardiogram was being made and remained constant from then on. At the time of this abrupt transition there was no change in the patient's clinical condition.

PROGRESSIVE BUNDLE BRANCH BLOCK

In most cases of established bundle branch block the condition is probably progressive from sinus rhythm to complete block of the branch, as in most cases the etiologic factor is undoubtedly coronary

106a Since this paper went to press an excellent article by Comeau, Hamilton and White has appeared (Comeau, W. J., Hamilton, J. G. M., and White, P. D. Paroxysmal Bundle-Branch Block Associated with Heart Disease, *Am Heart J* **15** 276, 1938). Another case has also been reported, by Bishop (Bishop, L. F., Jr. Transient, Recurrent, Complete Left Bundle-Branch Block, *ibid* **15** 354, 1938).

107 Perry, C. B. Observed Onset of Bundle-Branch Block with Coronary Thrombosis Forty-Five Hours Later, *Am Heart J* **9** 642, 1934.

108 Hollingsworth, E. W. Personal communication to the author.

arteriosclerosis and the lesions of the bundle branches are gradual to the point of complete destruction at one or more points. Such progression has been observed in many cases. An illustrative case is that reported by Krumbhaar¹⁰⁹ (1917, case 3), in which progressive establishment of bundle branch block was noted, with the occurrence of occasional aberrant beats during the different stages. Other instances were those reported by Hyman and Parsonnet¹¹⁰ (1930). These authors described 5 cases, 4 of which began with the curve typical of left axis deviation and an inverted T wave in lead I and later changed to the curve typical of left bundle branch block and 1 of which began with the curve of right axis deviation and later changed to the curve typical of right bundle branch block. In the first case the sinus rhythm persisted, in the second case auricular fibrillation developed with the block of the branch, in the third case complete auriculoventricular block appeared with the bundle branch block complex, and in the fourth case extrasystoles arising from multiple foci occurred after the establishment of bundle branch block. Willius¹¹¹ (1933) described several cases of progressive myocardial disease in which the electrocardiogram showed progressive change to bundle branch block. In his third case the first tracings showed "left ventricular preponderance", nine months later the T wave in lead I was inverted, and the QRS wave was slightly notched and showed a duration of 0.12 second, four months after this the changes were more marked, and necropsy showed marked coronary arteriosclerosis and myofibrosis. In his fifth case the first electrocardiogram showed "left ventricular preponderance," with an inverted T wave in lead I, the second tracing, made nine months later, showed inversion of the T wave in leads I and II, and one year after this the curves were typical of left bundle branch block. His sixth case was one of acromegaly with hyperthyroidism and cardiac hypertrophy, in which the first tracing showed "left ventricular preponderance" and the second tracing made four months after subtotal thyroidectomy showed typical left bundle branch block, the patient being then more dyspneic.

BUNDLE BRANCH BLOCK ASSOCIATED WITH IMPAIRED AURICULOVENTRICULAR CONDUCTION

Many cases are on record in which the form of the ventricular complex in the presence of auriculoventricular block was of the bundle branch type. In a number of these cases tracings made at different

109 Krumbhaar, E. B. Transient Heart-Block. *Electrocardiographic Studies*, Arch Int Med **19** 750 (May) 1917.

110 Hyman, A. S., and Parsonnet, A. E. Bundle Branch Block. The Phenomenon of Its Development in Relation to Axis Deviation of the Heart, Arch Int Med **45** 868 (June) 1930.

111 Willius, F. A. The Progression of Myocardial Disease as Recorded by Serial Electrocardiograms, M. Clin North America **16** 1493, 1933.

times or the same tracing showed shifts, abrupt or gradual, in the form of the ventricular complex from that of right to that of left bundle branch block or intermediate forms. In some of these cases the idio-ventricular rhythm was rapid, indicating probably an irritative as well as a destructive lesion in the branch in which the new automatic pace-maker was located.

In the section entitled "Review of Clinical Studies of Permanent Bundle Branch Block" the number of cases of bundle branch block associated with auriculoventricular block was noted in each series of cases in which the author included this feature in his report. Cornell, Claytor and I¹¹² (1936) have reviewed this subject, listing the reports of such cases obtained from the literature and reporting 3 cases of our own, with detailed histopathologic studies. We concluded that the pathogenic factor in all these cases is probably disease of the coronary arteries and that the condition is due usually to lesions, partial or complete, in both bundle branches in most instances, although we considered that destructive lesions of the terminal portion of the bundle of His may also produce such varying ventricular complexes. We stated that in cases of auriculo-ventricular heart block due to bilateral bundle branch lesions the form of the ventricular complex is frequently suggestive of bundle branch block and that variation in the form of this complex is common.

These variations suggest a shift in the site of the pace-maker, sometimes from one side of the septum to the other. The ventricular complexes may be of supra-ventricular form however, and then there are either two pace-makers, one in each bundle branch, generating impulses simultaneously, or, more probably, a single pace-maker in one or the other branch sending impulses directly through the interventricular septum into the Purkinje network of the contralateral ventricle as well as into that of the homolateral ventricle.

VENTRICULAR PREPONDERANCE, VENTRICULAR STRAIN AND EFFECT OF CARDIAC POSITION ON THE ELECTROCARDIOGRAM

Since Lewis¹¹³ (1914) and Cotton¹¹⁴ (1917) first studied the effect of ventricular hypertrophy on the electric axis of the electrocardiogram a number of other excellent studies have been made (Bridgman,¹¹⁵ 1915, Carter, Richter and Greene,¹¹⁶ 1919, Pardee,¹¹⁷ 1920,

112 Yater, W. M., Cornell, V. H., and Claytor, T. Auriculoventricular Heart Block Due to Bilateral Bundle-Branch Lesions. Review of the Literature and Report of Three Cases with Detailed Histopathologic Studies, *Arch Int Med* 57 132 (Jan) 1936.

113 Lewis, T. Observations upon Ventricular Hypertrophy, with Especial Reference to Preponderance of One or Other Chamber, *Heart* 5 367, 1913-1914.

114 Cotton, T. F. Observations upon Hypertrophy, *Heart* 6 217, 1917.

115 Bridgman, E. W. The Value of the Electrocardiogram in the Diagnosis of Cardiac Hypertrophy, *Arch Int Med* 15 487 (March) 1915.

Dieuaide,¹¹⁸ 1921, Herrmann and Wilson,¹¹⁹ 1922, White and Burwell,¹²⁰ 1924, Reid,¹²¹ 1928, Wilson and Herrmann,¹²² 1930, Master,¹²³ 1930, Proger and Davis,¹²⁴ 1930) Ventricular preponderance, ventricular strain and the effect of the cardiac position on the electrocardiogram are subjects that have somewhat beclouded the subject of bundle branch block or disturbances of intraventricular conduction. This is true more particularly in cases in which there is slight prolongation of the QRS complex and in cases in which there is negativity of the T wave. In this connection the conclusions of Herrmann and Wilson¹¹⁹ (1922) are worthy of quotation:

The relative weight of the two ventricles is but one of many factors which influence the form of the ventricular complex of the electrocardiogram. Its influence predominates only when the heart is greatly hypertrophied. There is no definite relation between the form of the ventricular complex and the relative weight of the two ventricles when the ventricular weight is below 250 grams. The chief factors which disturb the relation between the form of the electrocardiogram and the relative weight of the two ventricles, so it is suggested, are (1) variations in the position of the heart, (2) variations in the arrangement of the ventricular conducting system, and (3) disturbances of intraventricular conduction. The form of the normal electrocardiogram is not determined by the relative weight of the two ventricles; it is chiefly dependent upon the position of the heart and upon the arrangement of the ventricular conducting system, sometimes one, sometimes the other, of these factors exerts the greater influence.

In a later study Wilson and Herrmann¹²² (1930) made further observations on this problem, with the following conclusions:

Comparison of the QRS interval and the ventricular weight indicates that the length of this interval increases in average value with the cube root of the

116 Carter, E. P., Richter, C. P., and Greene, C. H. A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram, *Bull. Johns Hopkins Hosp.* **30**: 162, 1919.

117 Pardee, H. E. B. The Determination of Ventricular Predominance from the Electrocardiogram, *Arch. Int. Med.* **25**: 683 (June) 1920.

118 Dieuaide, F. R. The Determination and Significance of the Electrical Axis of the Human Heart, *Arch. Int. Med.* **27**: 558 (May) 1921.

119 Herrmann, G. R., and Wilson, F. N. Ventricular Hypertrophy. A Comparison of Electrocardiographic and Post-Mortem Observations, *Heart* **9**: 91, 1922.

120 White, P. D., and Burwell, C. S. The Effects of Mitral Stenosis, Pulmonic Stenosis, Aortic Regurgitation and Hypertension on the Electrocardiogram, *Arch. Int. Med.* **34**: 529 (Oct.) 1924.

121 Reid, W. D. Comparison of the Electrical Axis Shown by the Electrocardiogram with Roentgen Mensuration of the Heart, *Am. Heart J.* **4**: 223, 1928.

122 Wilson, F. N., and Herrmann, G. R. Relation of QRS-Interval to Ventricular Weight, *Heart* **15**: 135, 1930.

123 Master, A. M. Characteristic Electrocardiograms and Roentgenograms in Arterial Hypertension, *Am. Heart J.* **5**: 291, 1930.

124 Proger, S. H., and Davis, D. The Significance of Axis Deviation in the Human Electrocardiogram, *Arch. Int. Med.* **45**: 975 (June) 1930.

ventricular weight. Comparison of the QRS interval and the thickness of the left ventricular wall shows a similar increase in the average value of this interval with an increase in muscle thickness. QRS intervals which exceed 0.10 second should not in general be ascribed to increased size of the heart or to increased thickness of the left ventricular wall alone, but to retarded intraventricular conduction.

The occasional observations, some of which have previously been alluded to, of the progression of the electrocardiographic picture of left axis deviation, with or without a slightly prolonged QRS interval and with or without inversion of the T wave in lead I, to the typical electrocardiographic picture of bundle branch block add considerable support to the conclusions of these authors.

The excellent paper of Barnes and Whitten¹²⁵ (1929) entitled "Study of T-Wave Negativity in Predominant Ventricular Strain" fails to take into account the possibility of lesions of the bundle branches in producing negativity of the T wave. These authors have shown that "in cases in which the strain was thrown predominantly on the left ventricle" there was often inversion of the T wave in lead I or in leads I and II, that "in cases in which the condition produced disproportionate load on the right ventricle" the T wave was often inverted in leads II and III, and that "in conditions in which multiple lesions compete for maximal strain on the two ventricles, the leads in which the T waves will be inverted cannot be predicted." These conclusions, logical as they seem, for the very reason that no account is taken of the influence of possible lesions of the bundle branches, indicate the need for more extensive study of the histologic structure of the conduction system in cases of negativity of the T wave.

The effect of the position of the heart on the form of the electrocardiogram has been studied by many authors since Einthoven and associates'¹²⁶ original publication on the subject in 1913. Noteworthy studies of this subject have been those of Waller¹²⁷ (1914), White and Bock¹²⁸ (1918), Cohn¹²⁹ (1922), Meek and Wilson¹³⁰ (1925),

125 Barnes, A. R., and Whitten, M. B. Study of T-Wave Negativity in Predominant Ventricular Strain, *Am Heart J* 5 14, 1929.

126 Einthoven, W., Fahr, G., and de Waart, A. Ueber die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, *Arch f d ges Physiol* 150 275, 1913.

127 Waller, A. D. The Various Inclinations of the Electrical Axis of the Human Heart. 1A. The Normal Heart, Effects of Respiration, *Proc Roy Soc, London*, s B 88 49, 1914.

128 White, P. D., and Bock, A. V. Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, *Am J M Sc* 156 17, 1918.

Jones and Roberts ¹³¹ (1929), Ackerman and Katz ¹³² (1933), Kissin, Ackerman and Katz ¹³³ (1933), Kountz, Prinzmetal, Pearson and Koenig ²² (1935), and Alexander and Bauerlein ¹³⁴ (1936), from which it may be concluded that, while the position of the heart affects the form of the electrocardiogram, mainly in regard to its electric axis, this factor is of little practical significance in connection with the curves in cases of bundle branch block, provided there is no extensive juxta-cardiac lesion which would greatly alter the position of the heart and provided the patient is in the ordinary sitting or supine position during the making of the electrocardiogram

The important questions arising out of these observations are When is right or left axis deviation with a slightly prolonged QRS interval indicative of early bundle branch lesions, provided the position of the heart is normal? Is the additional presence of negativity of the T wave a definite sign of disturbance of function of a bundle branch? These questions can be answered only after extensive histopathologic study of the conduction systems of many hearts

HISTOPATHOLOGIC STUDIES OF BUNDLE BRANCH BLOCK REPORTED IN THE LITERATURE

Thus far I have discussed bundle branch block purely from the standpoint of the experimental evidence of its nature and the electrocardiographic and clinical manifestations. Just as the concept from this point of view has varied so much, likewise the data concerning the histopathologic basis of this problem have been conflicting, incomplete and relatively scanty. Much less certainty, in fact, exists on this point because of the tremendous amount of labor required in the histologic study of the conduction system of one heart, the technical difficulties involved and the amount of experience necessary for evaluation of

129 Cohn, A. E. An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, *Heart* **9** 312, 1922

130 Meek, W. J., and Wilson, A. The Effect of Changes in Position of the Heart on the QRS Complex of the Electrocardiogram, *Arch Int Med* **36** 614 (Nov) 1925

131 Jones, H. W., and Roberts, R. E. The Electrical Axis of the Heart As an Indication of Changes in Ventricular Predominance, *Quart J Med* **23** 67, 1929

132 Ackerman, W., and Katz, L. N. Reversal in Direction of the QRS Complex of Experimental Right Bundle-Branch Block with Change in the Heart's Position, *Am Heart J* **8** 490, 1933

133 Kissin, M., Ackerman, W., and Katz, L. N. The Effect of the Heart's Position on the Electrocardiographic Appearance of Bundle-Branch Block in Man, *Am J M Sc* **186** 721, 1933

134 Alexander, H. L., and Bauerlein, T. C. The Influence of Posture on Partial Heart-Block, *Am Heart J* **11** 223, 1936

the findings. Few persons have had extensive experience in this field of research, and even their conclusions are extremely at variance.

For a study of every portion of the microscopically recognizable portion of the conduction system usually between 4,000 and 6,000 serial sections are required depending mainly on the size of the heart. Furthermore, in order for the reader to be able to judge of the merits of the work, not only must the writer carefully describe his findings, but he should also reproduce photomicrographs and electrocardiograms.

A careful review of the literature up to 1930 by Mahaim²⁶ revealed reports of only 19 cases involving the electrocardiographic diagnosis of bundle branch block in which anatomic studies had been made. Mahaim considered only 3 of these cases sufficiently well studied histologically to be accepted as convincing (Eppinger and Stoerk,¹³⁵ 2 cases, 1910, Kauf,¹³⁶ 1 case, 1924) and a fourth case as probably correctly evaluated (Fredericia and Moller,¹³⁷ 1918). The authors stated that lesions were observed in the right bundle branch and not in the left; the electrocardiograms had shown right bundle branch block, according to the original terminology. Even with Mahaim's rigid criteria, these 4 cases are open to criticism. The 2 cases of chronic aortic valvulitis with congestive failure reported by Eppinger and Stoerk were presented without photomicrographs and with only brief histologic descriptions, furthermore, the left bundle branch was said to be entirely unaffected in both—the correctness of this statement is doubtful, since it must be rare to find one branch seriously diseased without some involvement of the other. Kauf's case was also one of disease of the aortic valves (stenosis with calcification), the description of the microscopic study was brief, and the left bundle branch was said to be entirely normal. In the case of degenerative heart disease reported by Fredericia and Moller there had been frequent changes in the form and direction of the ventricular complex but no curve showing definite bundle branch block of either side. The authors described briefly marked fibrosis of the left bundle branch but none of the right, a remarkable observation in view of the electrocardiographic features.

Among the 15 other cases reviewed by Mahaim, there were 3 in which a histologic study of the conduction system was not made (2 cases reported by Lutembacher¹³⁸ [1926] apparently of coronary arterio-

135 Eppinger, H., and Stoerk, O. Zur Klinik des Elektrokardiogramms, *Ztschr f klin Med* **71** 157, 1910.

136 Kauf, E. Zur Diagnose des Schenkelblocks beim menschlichen Herzen *Ztschr f klin Med* **98** 126, 1924.

137 Fredericia, L. S., and Moller, P. Ein Fall von auf das Septum lokalisierter Myocarditis mit eigentümlichen Abnormitäten im Elektrokardiogramm, *Deutsches Arch f klin Med* **126** 247, 1918.

138 Lutembacher, R. Coronarite et infarctus sous-endocardiques a forme embolique, *Arch d mal du cœur* **19** 505, 1926, Coronarite et artérites du pancréas, troubles de conduction et diabète, *ibid* **19** 522, 1926.

sclerosis, both including disturbance of auriculoventricular conduction and 1 case of right and the other of left bundle branch block, 1 case reported by Parkinson and Bedford¹³⁹ [1928] of multiple myocardial infarcts, with the electrocardiographic curve showing left bundle branch block)

Four cases reported by Carter⁵ were incompletely studied histologically by Cohn and Lewis¹⁴⁰ (1914) largely because the tissue which was sent them was not adequate. In the case of chronic aortic and mitral valvulitis reported by von Wyss¹⁴¹ (1911) and studied histologically by Gerhardt,¹⁴² there were disturbances of auriculoventricular conduction, with the curve typical of left bundle branch block, but only one lead of the electrocardiogram was reproduced, Gerhardt observed partial lesions of both branches. The findings were therefore inconclusive.

Carter,⁵³ in 1918, revised his ideas somewhat concerning bundle branch block, as the result of a study of a case in which the electrocardiographic complexes were similar to those described by Oppenheimer and Rothschild²⁹ as indicative of arborization block. In general the curve resembled that typical of right bundle branch block but with low amplitude except during paroxysms of tachycardia, when the amplitude was high. The histologic study, made by van der Stricht, was not complete, since only a number of isolated blocks of tissue were examined. These showed localized areas of fibrosis in the main stem and in the posterior division of the left bundle branch.

The 2 cases reported by Oppenheimer and Pardee⁷ (1920) were described in abstract form with extremely little detail and no illustrations. One was said to be a case of left bundle branch block with lesions confined to the right bundle branch, and the other was said to be a case of right bundle branch block with lesions confined to the left bundle branch. From these data the authors questioned the accuracy of interpretation of electrocardiograms in cases of bundle branch block.

Drury¹⁴³ (1921) made an incomplete histologic study of a case of auricular flutter in which the curve was suggestive of right bundle branch block of low voltage, owing to chronic coronary occlusion.

Waldorp's¹⁴⁴ case (1924) can hardly be called one of bundle branch block, and the histologic study was not convincingly described.

139 Parkinson, J, and Bedford, E. Cardiac Infarction and Coronary Thrombosis, *Lancet* **1** 4, 1928.

140 Cohn, A. E., and Lewis, T. The Pathology of Bundle Branch Lesions of the Heart, *Proc New York Path Soc* **14** 207, 1914.

141 von Wyss, W. Beitrage zur der Klinik des Elektrokardiogramms, *Deutsches Arch f klin Med* **103** 505, 1911.

142 Gerhardt, D. Klinische und anatomische Beitrage uber Adams-Stokes'sche Krankheit und Vagusbradykardie, *Deutsches Arch f klin Med* **106** 462, 1912.

143 Drury, A. Arborization Block, *Heart* **8** 23, 1921.

144 Waldorp, C. P. Bradyarrhythmie dans une fibrillation auriculaire, *Rev Assoc méd argent* **37** 74, 1924.

Wenckebach and Winterberg¹⁴⁵ (1927) described a case of intermittent auriculoventricular heart block of varying degree in which there were variable ventricular complexes, the complex indicative of right bundle branch block predominating. The histologic study showed multiple lesions of the left bundle branch, the right branch could not be studied because of technical difficulties.

Marvin¹⁴⁶ (1928) described a case of left bundle branch block with tachycardia in which, after overdosage of digitalis, crises of polymorphic ventricular tachycardia of the alternating type occurred. The histologic study of the large, probably hypertensive, heart was incomplete.

The case reported by Taussig¹⁴⁷ (1929) cannot properly be called one of left bundle branch block because the electrocardiogram showed ventricular tachycardia. Also, the histologic study was incomplete.

Agostoni¹⁴⁸ (1929) studied a case in which the electrocardiogram showed left bundle branch block. By studying serial sections he observed patchy fibrosis of the myocardium, with the bundle of His and the left bundle branch normal but with the right bundle branch interrupted at two points by fibrous lesions.

Hill⁶² (1930) studied 2 cases of left bundle branch block histologically. In 1 case, however, he lost the right bundle branch 3 mm below its origin and observed no lesions in the conduction system except a few small round cells in that branch. In the other case he lost the right branch in its upper half, but he said he thought it divided into two branches before he lost it, one branch passing deeply into the myocardium. He did not find lesions in the conduction system, but there was diffuse myocardial fibrosis.

In 1930 Oppenheimer and Oppenheimer¹⁴⁹ reported in abstract form their histologic data in 10 cases of intraventricular block, "including bundle-branch block and arborization block." The third and tenth cases were the cases previously reported by Oppenheimer and Pardee.⁷ There were 5 cases of bundle branch block, 2 being cases of typical bundle branch block of the common discordant type and 3 being cases in which the electrocardiogram approached this type but was not per-

145 Wenckebach and Winterberg,⁸⁸ p. 349

146 Marvin, H. M. Paroxysmal Ventricular Tachycardia with Alternating Complexes Due to Digitalis Intoxication, *Am Heart J* 4: 21, 1928

147 Taussig, H. B. A Case of Bundle-Branch Block Confirmed by Pathological Study, *Bull Johns Hopkins Hosp* 45: 40, 1929

148 Agostoni, G. Un cas de lésion de la branche droite du faisceau de His, soupçonnée cliniquement, diagnostiquée par l'électrocardiogramme et contrôlée à l'autopsie, *Arch d mal du cœur* 22: 577, 1929

149 Oppenheimer, B., and Oppenheimer, E. The Site of the Cardiac Lesion in Ten Cases of Interventricular Block Including Bundle-Branch Block and Arborization Block, *Tr A Am Physicians* 45: 427, 1930

fectly characteristic. In all 5 cases the histologic lesion was on the left side, and the right branch was intact except for a partial lesion in 1 case. Four other cases were instances of so-called arborization block. In all 4 the lesion involved the left bundle branch, "while the right branch was found to be intact throughout its course." The remaining case was one of "well-marked intraventricular block of the exceptional discordant type, in which the main ventricular deflection was directed downward in lead 1 and upward in lead 3. The lesion in this case was found solely in the right bundle branch, the left branch being normal throughout its course." These results unequivocally support the new concept of bundle branch block. Surprisingly, however, in all but 1 case the opposite bundle branch was intact. Furthermore, these authors did not publish clinical histories, electrocardiograms, necropsy reports, descriptions of the histologic studies or photomicrographs in connection with any of the cases.

In 1931 Mahaim's²⁶ splendid volume on the organic diseases of the conduction system was published. Mahaim's thorough study of 8 cases of bundle branch block (7 right and 1 left, according to the original terminology) supported the original terminology, but in every case the lesions, mainly fibrosis due to vascular disease, were present in both bundle branches, although they were more nearly completely interruptive in the branch assumed, on the basis of the electrocardiogram, to be blocked. Electrocardiographically these were all cases of so-called intraventricular block, but in most of them there were differences from the original clinical criteria of bundle branch block, mainly in regard to amplitude, spread of the QRS complex and notching. In 2 cases the amplitude was small, the electrocardiograms resembling those of so-called arborization block. One case (observation XI) was an instance of complete heart block, with ventricular tachycardia and right bundle branch block. In cases 5, 6, 8, 9 and 10 there was a deep S deflection in lead I. The only important point open to doubt in Mahaim's study was the interpretation of the branch more severely affected, since serious lesions were present in both branches in all cases. Mahaim stressed the importance of studying the branches by serial sections as far down as they can be recognized, since in some of the cases he observed the important lesion in the lowermost part of the right branch. He made a strong point of the blood supply of the bundle branches, emphasizing the common source of supply of the right branch and the anterior division of the left, explaining thus the bilaterality of lesions and the escape of the posterior division of the left branch in many cases. Although Mahaim's work further beclouds the problems involved, it is of great value because it provides a careful review of the literature, it points out the necessity of thorough histologic study of the conduction system,

it emphasizes the usual bilaterality of lesions and their frequent vascular pathogenesis and it gives the author's thought-provoking deliberations

In 1935 Mahaim,¹⁵⁰ reporting a study of 2 cases of right bundle branch block, reviewed his previous cases and eliminated all but 2 of his 7 cases as being indecisive. He excluded observation V because of the short period of clinical observation (two and a half months), an elongated PR interval and lesions of the common trunk. Observation VI was questioned because of the short period of clinical control (three weeks). Observation IX was discarded because of the short period of clinical study, the wide QRS complex and the multiple and bilateral lesions and because only one tracing had been made. Observation X was eliminated for the same reasons plus the presence of auricular fibrillation. Observation XI was excluded for similar reasons, "total bilateral lesions rendering the case problematical." Finally, he discarded observation XII because there was only a single tracing and because of the extended bilateral lesions without complete interruption of the left bundle branch, which he said he believed the electrocardiogram indicated. His criteria for determining which bundle branch influences the form of the electrocardiogram in bundle branch block had become much stricter. He said he considered as essential (1) prolonged clinical observation, with numerous electrocardiograms, (2) a constant, easily measurable and not prolonged PR interval, (3) the absence of tachycardia, auricular fibrillation, disturbances of auriculoventricular conduction and notably (4) the existence of no more than a slight prolongation of the QRS complex, since increases of over 0.1 second are due to extensive lesions of both bundle branches. If the anatomic lesions are clearcut, one does not need to be so rigorous about the clinical features, such as the length of the period of clinical control. He pointed out that the lesions of the bundle branches are almost always bilateral, which is the greatest source of error of interpretation, and that one cannot always be sure of the conductivity of a few fibers which might appear intact in a severely diseased branch. He stressed the point that if 1 of 10 sections shows definite lesions, one should stain and study some of the intervening sections also.

His new cases were interesting. Observation I concerned a man of 31 who had severe rheumatic lesions of the aortic and mitral valves and some tricuspid valvulitis. He had been followed eleven years. At first there was a normal electrocardiogram, then auricular fibrillation with slight right axis deviation and during the last six years auricular

¹⁵⁰ Mahaim, I. Nouvelles recherches sur les lésions du faisceau de His-Tawara, le bloc de branche gauche et sa pathogénie, la septite mitrale, *Ann de méd* 38 185, 1935

fibrillation and right bundle branch block, with QRS never longer than 0.1 second, the T wave was almost iso-electric. In a thorough histologic study he observed severe generalized fibrotic lesions of the left branch from its origin. The bundle of His and the right bundle branch were only slightly affected. There was extensive scarring of the interventricular septum and of the endocardium of the left ventricle. Observation II concerned a man of 38 who had been observed for six months. There had existed during this time an irreducible auricular flutter with two to one block except during paroxysms of one to one rhythm brought about by effort. The heart rate was usually 120 per minute but at times 240. There was right bundle branch block, with a QRS interval of 0.11 second. Severe mitral stenosis and tricuspid valvulitis were observed at necropsy, with dilatation of the pulmonary artery and functional pulmonary insufficiency, the foramen ovale was widely patent. Complete interruption of the left bundle branch at its origin was noted, but there were also extensive fibrous and inflammatory lesions of the right branch due to "septitis of mitral origin." There were also serious hemorrhagic lesions of the right branch of recent origin.

In this same article Mahaim also pointed out that one must look carefully for a large offshoot of the posterior part of the uppermost portion of the left bundle branch. This branch, originally described by him,¹⁵¹ in 1932, under the title "*Le bloc bilatéral manqué*," is supposed to arise high up near the bifurcation of the bundle of His and to pass directly into the septal myocardium, so that even complete lesions of the left bundle branch a little lower would not produce bundle branch block. In the patient in whom he discovered this offshoot there was active and healed septal myocarditis, with complete and extensive destruction of the left bundle branch and complete interruption also of the right bundle branch, but idioventricular rhythm did not result. Instead, there were a PR interval of 0.16 second, a QRS complex of 0.14 second, with low voltage and multiple notching, and a small slightly diphasic T wave. The main ventricular complex was upright in lead I but triphasic in lead III. The curves resembled those of "arborization block," and Mahaim concluded that such curves can be due to complete lesions of both bundle branches. He said he believed that the newly discovered connections can explain all discrepancies among the observations of various investigators and the various degrees of enlargement of QRS. The more extensive the lesion of the left bundle branch, the wider the QRS complex should be, since the excitation wave passing into the septal myocardium through the high offshoot would have a

151 Mahaim, I. Nouvelles recherches sur les lésions du faisceau de His-Tawara, le bloc bilatéral manqué, nouvelle forme anatomique de bloc du cœur à substituer au bloc dit "d'arborisations," *Ann de med* 32 347 1932

longer course to follow in the more slowly conducting myocardium until it reached healthy elements of the Purkinje system much farther down

Meessen¹⁵² (1935), studying the fetal calf heart, was unable to find connections through the interventricular septum between the two bundle branches or their network, as had been demonstrated by Cardwell and Abramson¹⁵³ (1931) and Wahlin¹⁵⁴ (1932). In 2 human hearts he could not verify the special superior and posterior connections of the left branch with the septum, as described by Mahaim in 1, but in the other he found many fine connections from the left branch to the septum. In 1 case the curves were typical of "arborization block" of the right bundle branch. Meessen found the conduction system intact down to the ramifications and conceived that the myocardium was cut off from the Purkinje network by fibrosis. In the other the curves were those of right bundle branch block, but there was myeloid infiltration of the left branch.

For the sake of completeness one should call attention to the work of Rosenthal¹⁵⁵ (1932), who studied the conduction system of 5 hearts histologically but did not give details of his technic or of his studies. In 1934 Géraudel,¹⁵⁶ who has made numerous but apparently incomplete microscopic studies, stated that there are no bundle branches or arborizations but that the main bundle crosses the fibrous septum and is lost immediately in the interventricular septum.

In 1936 Cornell, Clayton and I¹¹² reported 3 cases of auriculoventricular heart block due to bilateral bundle branch lesions, with detailed histologic studies of the conduction system. In the first case the electrocardiogram showed curves of essentially supraventricular type, and there were fibrotic lesions practically completely interrupting both bundle branches. In the second case the curves were typical of left bundle branch block, the upper half of the entire left bundle branch was almost completely replaced by dense fibrous tissue, and about one third of the cross-section of the right branch was replaced by fibrous tissue in the upper third of the branch. In the third case the curves showed complexes varying from that of right to that of left bundle

152 Meessen, H. Zur normalen Histologie des Reizleitungssystems und zu seinen Störungen, *Ztschr f Kreislaufforsch* **27** 42, 1935

153 Cardwell, J. C., and Abramson, D. I. The Atrioventricular Conduction System of the Beef Heart, *Am J Anat* **49** 167, 1931

154 Wahlin, B. Die interventrikularen Verbindungen im Reizleitungssystem des Herzens, *Upsala Lakaref. förh* **38** 1, 1932

155 Rosenthal, S. R. Branch Arborization and Complete Heart Block, *Arch Int Med* **50** 730 (Nov) 1932

156 Géraudel, E. Le faisceau de His est un connecteur septo-septal, inexactitude du schéma de Tawara, *Ann d'anat. path* **11** 300, 1934

branch block on different occasions, about 60 per cent of the track of the left bundle branch was replaced by fibrous tissue, and about 75 per cent of the cross-section of the right branch was likewise affected

SUMMARIES OF SIXTEEN CASES OF BUNDLE BRANCH BLOCK STUDIED PATHOLOGICALLY

Before proceeding to a more detailed description of the 6 cases which constitute the main subject matter of this report, it would be of some value briefly to review the clinical records and gross morbid anatomic data for the 16 cases of bundle branch block that have been studied, as reports of pathologic studies of such cases are rare in the literature

CASE 1 (previously reported as case 1 by Yater, Cornell and Claytor,¹¹² 1936) — A man aged 65 years had dyspnea on exertion and spells of dizziness, faintness and unconsciousness for more than a year before death. Complete heart block was known to have existed for three months before death, which occurred in an Adams-Stokes attack. Electrocardiograms showed left axis deviation and did not suggest bundle branch block, although the histologic lesions were confined to the bundle branches, the auriculoventricular node and bundle being uninvolved. The blood pressure was 160 systolic and 60 diastolic. The heart weighed 450 Gm. The myocardium appeared to be normal. The anterior descending coronary artery was sclerotic, and about 3 cm from its origin it was constricted to about one quarter of its normal caliber. The other coronary arteries were somewhat thickened, but their lumens were of normal diameter. The endocardium and valves appeared normal. The pathogenesis of the bilateral bundle branch block was undoubtedly due to coronary arteriosclerosis.

CASE 2 (previously reported as case 2 by Yater, Cornell and Claytor,¹¹² 1936) — A man aged 63 years had had Adams-Stokes attacks for nearly four years. The blood pressure was 110 systolic and 60 diastolic. Electrocardiograms made at intervals during this period showed numerous changes in the ventricular complex. Before two to one heart block was established, the form was almost typically that of left bundle branch block. After two to one heart block had become established, the curves no longer typified bundle branch block. Finally, complete heart block supervened, with the reappearance of left bundle branch block. Death occurred during a prolonged convulsive seizure. The heart weighed 450 Gm. The large coronary arteries were not atheromatous or thickened, and their lumens were normal. The chambers were normal in size and not dilated. The myocardium showed no evidence of fibrosis grossly. The endocardium and valves appeared to be entirely normal. The cause of the histologic lesions of the conduction system, which consisted of fibrosis confined to the bundle branches (the left much more than the right), was coronary arteriosclerosis involving the small arteries in the interventricular septum, which were considerably thickened and narrowed in places.

CASE 3 (previously reported as case 3 by Yater, Cornell and Claytor,¹¹² 1936) — A man aged 49 years had some dyspnea on exertion and occasional dizzy spells for over a year before death. The blood pressure was 132 systolic and 88 diastolic. Thrombotic occlusion of the arteries of the right leg developed, and he died while under an anesthetic before amputation could be performed. Numerous electrocardiograms made during the last year of life showed varying degrees of auriculo-

ventricular heart block, with some periods of sinus rhythm. In all the electrocardiograms there was evidence of impaired conduction of one or the other bundle branch, more often of the left. The heart weighed 410 Gm. The large coronary arteries appeared normal, with an occasional small, slightly elevated atheromatous plaque. The myocardium was flabby and grayish red. In the posterior wall of the left ventricle near the apex and close to the septum there was a small scar, 0.8 cm in diameter, with fine yellow mottling. There was also suggestion of scarring in the interventricular septum near the base anteriorly. The endocardium and valves were apparently normal. The pathogenesis of the incomplete but severe fibrosis of the two bundle branches was, again, probably due to disease of the coronary arteries. The small intramyocardial arteries were surrounded by much more than the normal amount of fibrous connective tissue.

CASE 4 (case 1 of the present report) —This was a case of right bundle branch block. The heart weighed 400 Gm. There was healed mitral valvulitis, without much stenosis. The large and small coronary arteries were dilated and thin walled. There was complete destruction of the right bundle branch by a dense myocardial scar. A few small scars were present elsewhere.

CASE 5 (case 2 of the present report) —This was a case of right bundle branch block. The heart weighed 560 Gm. There was extreme mitral scarring, with stenosis. The aortic and tricuspid valves were slightly affected. The large coronary arteries were not very sclerotic. There was a large scar in the endocardium of the left upper half of the interventricular septum. The right bundle branch was completely replaced by fibrous tissue in part of its course, the left branch was compromised by endocardial fibrosis.

CASE 6 (case 3 of the present report) —This was a case of right bundle branch block, with paroxysms of various degrees of partial auriculoventricular block and asystole. The heart weighed 450 Gm. It was not dilated, but all the chambers were hypertrophied, especially the left auricle, right ventricle and interventricular septum. There was extensive thickening of the endocardium, especially over the upper half of the left side of the interventricular septum. The myocardium showed streaks of fibrosis, most marked in the septum. The coronary arteries and the valves were normal. Serial sections showed extreme fibrosis of the myocardium, partial destruction of the auriculoventricular bundle by fibrosis, complete replacement of the lower half of the right bundle branch by fibrous tissue, almost complete destruction of the left bundle branch and sclerosis of the media of the small coronary arteries.

CASE 7 (case 4 of the present report) —This was a case of "incomplete" left bundle branch block. The heart weighed 460 Gm. The left ventricle was hypertrophied. The coronary arteries were thin and dilated. The valves were normal. The myocardium was practically normal. Serial sections showed the right bundle branch to be moderately fibrotic, and the left branch showed extensive interstitial fibrosis.

CASE 8 (case 5 of the present report) —This was a case of "incomplete" left bundle branch block. The heart weighed 550 Gm and was dilated. There was severe coronary arteriosclerosis, with complete thrombotic occlusion of the anterior interventricular artery. There was an old healed infarct of the lower half of the interventricular septum and of the apical region of the left ventricle. The valves were normal. Serial sections showed moderate fibrosis of the midportion of the right bundle branch and severe compression of the left branch by fibrous tissue, with complete disappearance of the anterior division in the region of the infarct.

CASE 9 (case 6 of the present report) —This was a case of left bundle branch block. The heart weighed 575 Gm and was greatly dilated. There was not much coronary arteriosclerosis. The myocardium did not appear abnormal. The valves were normal. Serial sections showed small discrete scars in the myocardium. The auriculoventricular node and bundle were moderately fibrotic. There was moderate fibrosis of the first portion of the right bundle branch and moderate and variable interstitial fibrosis of the left branch.

CASE 10 (Army Medical Museum accession no 38706) —A man aged 43 years had been known to have a cardiac disorder for a year before death, with weakness, dyspnea on exertion and later progressive edema with orthopnea. The blood pressure was 106 systolic and 88 diastolic. An electrocardiogram showed left bundle branch block, without increase in amplitude of the ventricular complex. The heart weighed 490 Gm and was dilated. The anterior descending coronary artery was calcified, with great reduction in the size of the lumen and a recent red thrombus. The left circumflex artery was similar, but the right coronary artery, although sclerotic, had a good lumen. A large infarct involved the apex of the left ventricle, and the interventricular septum was thinned and scarred. The latter was covered by a much thickened endocardium. A mural thrombus filled the apex of the left ventricle. The valves appeared normal. A histopathologic study of the conduction system has not been made.

CASE 11 (Army Medical Museum accession no 40539) —A man aged 55 years began to have palpitation of the heart five years before he died and was told he had a large heart. For two years before death he had attacks of congestive heart failure. The heart was found to be large, and there was evidence of aortic regurgitation. The blood pressure was 164 systolic and 100 diastolic. Eight electrocardiograms made at intervals during the last eight months showed left bundle branch block, with little variation. The heart weighed 770 Gm and was dilated. The hypertrophied myocardium was streaked with fibrous tissue. The aortic valve was thickened, with rolled free edges, and the anterior cusps were fused by a mass of calcium at the commissure. There was also extensive calcification at the line of attachment of the posterior cusp. The other valves were essentially normal. There was severe coronary arteriosclerosis, especially of the anterior interventricular artery, which was nearly occluded by the sclerosis. Serial sections were made of the conduction system but were not satisfactory.

CASE 12 (Army Medical Museum accession no 40621) —A man aged 42 years had a cardiac attack suggestive of thrombosis of the coronary arteries two months before he died, which was the first indication of heart disease. The highest blood pressure was 145 systolic and 95 diastolic. Anginal attacks followed. Death occurred unexpectedly. An electrocardiogram showed "incomplete" left bundle branch block. The heart weighed 600 Gm. The anterior descending coronary artery was calcified and had a small lumen, which was filled with a recent thrombus. The right coronary artery was sclerotic but not occluded. There was a large healing infarct of the lower anterior wall and apical region of the left ventricle, and this area was covered by a large, flat mural thrombus. The valves appeared normal. A histopathologic study of the conduction system has not been made.

CASE 13 (Army Medical Museum accession no 41621) —A man aged 62 years began to have attacks of dyspnea and precordial pain three months before he died. There was evidence of pulmonary congestion. The blood pressure was 95 systolic and 70 diastolic. Five electrocardiograms were made and were similar, showing left bundle branch block without increased amplitude. The heart weighed 670 Gm, but the much thickened adherent pericardium probably accounted for 150 Gm.

The heart was considerably dilated. The coronary arteries were all sclerotic and more or less completely calcified. Each of the anterior and posterior interventricular arteries was occluded by the sclerosis in its distal half. There was a large partially healed infarct involving the lower and anterior half of the interventricular septum. This area was thin and bulged into the right ventricle, it was covered on the left ventricular surface by a friable grayish red lamellated thrombus. The apical region and the lower portion of the anterior wall of the left ventricle were involved in the infarction. The valves were essentially normal except for some atheromatosis of the aortic cusps and of the aortic leaflet of the mitral valve. Serial sections were made of the conduction system but were not satisfactory.

CASE 14 (Army Medical Museum accession no 42974) —A Negro aged 48 years had been dyspneic for six months and had had a cough with expectoration of blood. Paroxysmal nocturnal dyspnea had developed. The blood pressure was 150 systolic and 130 diastolic. An electrocardiogram showed left bundle branch block, with low amplitude in lead I. The heart weighed 155 Gm. There were scars in the interventricular septum, at the bases of the papillary muscles and in the apical region of the left ventricle. The anterior descending artery showed moderate sclerosis but not much diminution in the caliber of the lumen, the other coronary arteries were only mildly sclerotic. Serial sections of the conduction system were made but were not satisfactory.

CASE 15 (Army Medical Museum accession no 43235) —A man aged 79 years had had some dyspnea for seven years, and an electrocardiogram showed impaired auriculoventricular conduction at the beginning of that time. For about a year two years before death the heart rate varied a great deal but was often slow, being often as low as 28. An electrocardiogram made two years before death showed two to one heart block, a QRS interval of 0.14 second, a large R wave and a large notched S wave in the three conventional leads and an upright T wave in these leads. An electrocardiogram made a year before death showed complete heart block, the same QRS complex in lead I, a small notched R wave and a large notched S wave in lead II, no R wave but a deep slurred S wave in lead III, a large upright T wave in all three leads, occasional coupling of ventricular complexes and frequent ventricular extrasystoles. An electrocardiogram made a month before death showed sinus rhythm, with a PR interval of 0.22 second and typical left bundle branch block, with a QRS interval of 0.14 second. Death resulted from heart failure. The heart weighed 650 Gm. There was hypertrophy of both ventricles, especially the left. There was moderate sclerosis of the coronary arteries but no appreciable reduction in the caliber of their lumens. The aortic valve was calcified, and the right and left anterior cusps were fused. A spur of calcium extended downward a short distance from the right side of the calcified posterior cusp into the left ventricle in the interventricular septum. The other valves were essentially normal. There was no gross scarring of the myocardium. Serial sections of the conduction system were made but were not satisfactory.

CASE 16 (previously reported by Yater and Shapiro¹⁵⁷) —A woman aged 21 years had been told she had heart disease at the age of 7 years. There was a long harsh systolic murmur which was loudest at the left sternal border. Electrocardiograms showed left axis deviation, a variable direction of the T wave in

157 Yater, W. M., and Shapiro, M. J. Congenital Displacement of the Tricuspid Valve (Ebstein's Disease). Review and Report of a Case with Electrocardiographic Abnormalities and Detailed Histologic Study of the Conduction System, *Ann Int Med* 11:1043, 1937.

lead I and a QRS interval of 0.16 second. Death occurred unexpectedly during the night. The heart weighed 275 Gm and was typical of Ebstein's disease or congenital displacement of the tricuspid valve down into the right ventricle. The right side of the heart was greatly enlarged but not hypertrophied. Serial sections of the conduction system did not show lesions, but the course of the right bundle branch was somewhat anomalous.

ANATOMY OF THE CONDUCTION SYSTEM

The anatomic and histologic structure of the conduction system has been well described by Keith, His, Tawara, de Witt and others. The sino-auricular node (Keith-Flack), or pace-maker, is not of concern here. However, briefly, it is a relatively long flat bundle of small thin compact interlacing fibers in a groundwork of connective tissue, situated subepicardially just below the mouth of the superior vena cava, with its longitudinal axis in the sulcus terminalis. Its cross-section is fusiform or roughly triangular, and a comparatively large artery runs down the middle. There are also a number of arterioles in its substance, nerves and nerve ganglions are present subepicardially in its vicinity, and often nerves are seen at its edge. Rarely a nerve cell is seen in the substance of the node. The fibers of the node resemble myocardial fibers but are much smaller, they show cross-striations in good sections.

The auriculoventricular node (Tawara) lies close to the right side of the posterior portion of the central fibrous body, that is, in the right auricle a short distance anterior to the orifice of the coronary sinus and just above the attachment of the medial or septal cusp of the tricuspid valve. A relatively large artery with branches usually runs through it. This node resembles the sino-auricular node in structure but is not so compact and contains somewhat less connective tissue. Its fibers are slightly thicker, and their cross-striations are more frequently visible. They are arranged in whorls. At the beginning of the node, that is, in its most posterior portion, its fibers are looser at the periphery and merge with the auricular myocardium. In older persons there is often considerable fatty connective tissue adjacent to the node on its superficial surfaces.

After a short distance, roughly 0.5 cm, the node invades the central fibrous body and becomes the auriculoventricular bundle (Kent, His), without any definite line of demarcation. The bundle runs obliquely downward in the lower part of the central fibrous body to the lower edge of the membranous portion of the interventricular septum, being often separated by some fibrous tissue in its anterior part from the myocardium of the septum. It has no true sheath but is contained largely within the central fibrous body, which protects it. The fibers of the bundle are larger than those of the auriculoventricular node and

run in parallel bundles. They resemble more the ventricular fibers but do not contain so much myoplasm. The connective tissue framework is delicate, and there is no main artery but a number of arterioles and venules. Sometimes in older persons there is a fair amount of adipose connective tissue in the bundle.

The auriculoventricular bundle runs for about 1 to 1.2 cm and divides into right and left branches. The right branch appears to be more a continuation of the bundle and passes downward beneath the juncture of the medial and anterior leaflets of the tricuspid valve as a whitish threadlike process, at first being beneath the endocardium and not always distinctly separated from the surrounding cardiac muscle. A short distance down, about 0.5 cm, the branch comes to lie more deeply in the myocardium, where it runs in a cleft of connective tissue. After a variable distance, roughly 1 cm, it gradually works its way out along a cleft in the myocardium to the subendocardium again. Here it continues for about another 1 cm, spreading out to become a thin sheath of Purkinje fibers near the base of the anterior papillary muscle of the right ventricle, beyond which point it can rarely be recognized microscopically in the human heart. In its course it passes downward and anteriorly in the middle of the trabeculum of the ventricle, which corresponds to the moderator band of the beef heart. The fibers of the right branch are about the same size or a little larger than those of the myocardium, but they are usually paler. They are parallel and close together, and they often closely resemble the myocardial fibers. On cross-section the branch is variable in shape, being fusiform, oval, round or triangular in different portions.

The left bundle branch spreads out from the auriculoventricular bundle on the left side of the interventricular septum, at first as a thin layer of fibers. It is subendocardial throughout most of its course and becomes much thicker as it descends in the septum. It also gradually spreads out like a fan beneath the endocardium, and in the lower half of the septum it often divides into anterior and posterior divisions, one passing to the region of the base of the anterior papillary muscle and the other to the base of the posterior papillary muscle. In this region the Purkinje fibers rapidly spread out subendocardially among the usually numerous trabeculae and are no longer definitely recognizable. The endocardium is usually thicker in the upper part of the septum and contains discrete groups of smooth muscle fibers, which should not be mistaken for Purkinje fibers. Normally there is only a small amount of loose areolar connective tissue separating the bundle branch from the endocardium superficially and the myocardium deeply. The appearance of the fibers of the left branch in horizontal sections depends on the size of the heart and the degree of dilatation, as well

as on the portion of the septum being examined. These fibers are larger and much paler than myocardial fibers, containing a much less dense myoplasm. The myofibrils are more peripheral and more prominent, the cross-striations are usually readily observed but not as distinctly as in the myocardium. The Purkinje fibers become larger as the branch descends. Offshoots from the branch into the myocardium are practically never recognized in the human heart.

The vascularization of the conduction system has been capably studied, notably by Haas¹⁵⁸ (1911), Tandler¹⁵⁹ (1913), Gross¹⁶⁰ (1921), Mouchet¹⁶¹ (1922), Craiciianu¹⁶² (1922) and Spalteholz¹⁶³ (1924). The auriculoventricular node and bundle are supplied with blood almost entirely by one special artery, the ramus septi fibrosi, or the first posterior perforating artery, which passes forward into the auriculoventricular septum from the origin of the posterior descending, or interventricular, artery just at the point posteriorly where the two auricles and two ventricles meet. In approximately 90 per cent of hearts this is a branch of the right coronary artery, from the posterior extremity of its left circumflex branch, this artery then passing downward as the posterior descending artery. The anterior descending, or interventricular, artery may give a minor portion of the blood supply of the auriculoventricular bundle, especially in its anterior portion. As a rule the origin of the bundle branches also takes its main vascularization from this ramus septi fibrosi, but there are numerous variations. The vascular supply of the bundle branches is less positively known than that of the auriculoventricular node and bundle, but there is a general more or less definite arrangement. The arteries arise from the anterior and posterior descending, or interventricular, arteries and perforate the interventricular septum, passing toward its middle, where they anastomose to a certain extent. The left bundle branch, being spread out over the subendocardial surface of the left side of the septum and divided usually into an anterior and a posterior division, or ramification, has its blood supply both from the perforating septal branches of the anterior and from those of the posterior descending artery. In a general way the anterior perforating arteries supply the anterior divi-

158 Haas, G. Ueber die Gefassversorgung des Reizleitungssystems des Herzens, Anat. Hefte **43** 627, 1911.

159 Tandler, J. Anatomie des Herzens, Jena, Gustav Fischer, 1913.

160 Gross, L. The Blood Supply to the Heart, New York, Paul B. Hoeber, 1921.

161 Mouchet, A. Les arteres coronaires du cœur chez l'homme, Paris, Norbert Maloine, 1922.

162 Craiciianu, A. Anatomische Studien über die Coronararterien und experimentelle Untersuchungen über ihre Durchgangigkeit, Virchows Arch. f. path. Anat. **238** 1, 1922.

163 Spalteholz, W. Die Arterien der Herzwand, Leipzig, S. Hirzel, 1924.

sion of the left bundle branch, and the posterior perforating arteries supply the posterior division. The vascularization of the right bundle branch, a threadlike fasciculus, is not so definitely known but is most probably almost entirely derived from the perforating septal arteries of the anterior descending artery except, perhaps, in its terminal portion, which may receive some of its blood supply from the lower posterior perforating arteries. The upper third of the branch is probably supplied mainly by the two uppermost anterior perforating arteries and the middle third by a special branch of the second perforating artery, the ramus limbi dextri (Gloss). This same special artery probably nourishes most of the lower third of the branch. The anastomoses between the anterior and the posterior perforating arteries are probably very fine and not particularly effective in cases of sudden obstruction, as has been shown so well by Crainicianu. In slow obliteration these anastomoses are probably more efficacious in maintaining an adequate blood supply than in sudden occlusion.

Thus it is seen that the blood supply of the auriculoventricular node and bundle and of the posterior division of the left bundle branch comes mainly from the perforating septal arteries of the posterior descending, or interventricular, artery (in 90 per cent of the cases a branch of the right coronary artery), whereas the blood supply of the right bundle branch and of the anterior division of the left branch is almost entirely derived from the perforating septal branches of the anterior descending, or interventricular, artery.

HISTOLOGIC TECHNIC

A full time expert technician can properly prepare on the average 4 to 6 hearts per year for study of the conduction system. Unfortunately, at least 1 of these hearts must usually be discarded because of technical flaws due mainly to the difficulties of making thousands of uniformly good sections of a heart.

It is best not to keep a heart more than a few months, and the solution of formaldehyde employed should not be allowed to become more concentrated than a 1:10 dilution of the U. S. P. (40 per cent) solution. After the blocks of tissue have been embedded in paraffin, soaking them in water for from one to three weeks improves the quality of the cardiac muscle for sectioning. There is no specific stain for the conduction system, since the fibers are structurally very similar to those of the myocardium. In a fresh heart there may be more glycogen in the Purkinje fibers, but the use of some stain for glycogen, such as Best's carmine dye, is impracticable for routine work or extensive studies. Masson's trichrome stain gives the best coloring effects for study. The myocardium and conduction tissue are red, and connective tissue is green. In photomicrographs the parenchyma is dark, and the fibrous tissue is light, with a light red filter. Van Gieson's picrofuchsin stain is also good, but it fades after a time. This stains the parenchyma yellow and the connective tissue red, and in photomicrographs the parenchyma is light and the connective tissue dark.

The use of a dissecting microscope is invaluable for orientation and for studying so many sections, although a regular microscope must also be used frequently. The use of a dictaphone is time-saving when sections are being described.

It is vital to follow the bundle branches from beginning to end by means of serial sections, since one may not be able to identify them otherwise when they are the seat of lesions. This is especially true of the right branch, which is so small in diameter and so similar histologically to the myocardium that often it may not be definitely recognized in isolated sections, especially in its intramyocardial portion. It can be traced from below upward as well as from above downward, since in its lower subendocardial portion it is as easy to identify as it is from its origin in the bundle of His. However, lesions of the right branch are easier of interpretation than those of the left branch for the very reason that the right branch is so slender and readily studied in individual sections. When the left branch is diseased it sometimes happens that the isolated Purkinje fibers are difficult to distinguish from the fibers of the myocardium subjacent to the endocardium. This is especially true in the lower third of the interventricular septum, where the left branch is spreading out and dividing into smaller groups of Purkinje fibers. Purkinje fibers in the substance of the myocardium of the human heart are impossible to recognize but undoubtedly exist, just as they do in the hearts of large animals. There is considerable variation in the anatomic features of the left branch, the division into two portions about the middle of the septum, the anterior and the posterior, being often indefinite.

It is well not to make too many blocks from the septum but to make the blocks as large as possible and to include the whole thickness of the septum. Technicians complain but can usually make the sections satisfactorily if they are efficient. The branches are much more easily followed with fewer blocks. Usually 3 or 4 blocks can be cut to include the entire microscopically recognizable portion of the conduction system.

REPORT OF SIX CASES OF BUNDLE BRANCH BLOCK, WITH DETAILED HISTOPATHOLOGIC STUDY OF THE CONDUCTION SYSTEM

CASE 1¹⁶⁴ (Army Medical Museum accession no 46390) —*Clinical Record*— The patient was 50 years old at the time of his death on Feb 26, 1935. From his thirteenth year on he had lived a roving, dissipated life, changing occupations frequently, but apparently always making a "good living." In the course of his many occupations he had been a soldier, farmer and lineman. Until 1924 he had been in good health. Then he began to have dyspnea and lack of endurance. His blood pressure was first recorded in 1932, when it was 130 systolic and 82 diastolic. From that time there had been a steady increase in the blood pressure to 186 systolic and 136 diastolic shortly before death. He was first hospitalized with symptoms of cardiac embarrassment on Nov 6, 1934, and two days later the first electrocardiogram showed the presence of "incomplete" right bundle branch block. The heart was enlarged to the left as far as the anterior axillary line. A loud blowing systolic murmur was heard over the entire precordium but was loudest at the apex. The second heart sound at the apex was slightly reduplicated intermittently. Occasional premature beats were noted. There were three subsequent hospitalizations, all because of cardiac distress, which was more pronounced each

¹⁶⁴ Major John G Knauer gave me permission to use the records of this case and to study the heart.

time Enlargement of the liver was not detected until January 1935 Edema of the lower extremities was present only once, two weeks before death, although orthopnea and marked hepatic congestion had been present for three weeks Evidence of edema of the bases of the lungs was noted only in November 1934, otherwise edema was inconspicuous, and little was observed at necropsy

The entire illness was essentially due to chronic heart failure, although the actual terminal event was acute perforation of the duodenum at the site of an old peptic ulcer, with resulting general peritonitis A diagnosis of quiescent duodenal ulcer was made in March 1932, but symptoms referable thereto were almost negligible until the afternoon prior to the day of death

The electrocardiograms recorded on Nov 6 and 27, 1934, and on Jan 22, 1935, were in general similar The QRS complex measured 0.125 second and showed a deep S wave in lead I and an upright initial ventricular complex in lead III, with marked broadening and slurring or notching in all three conventional leads The

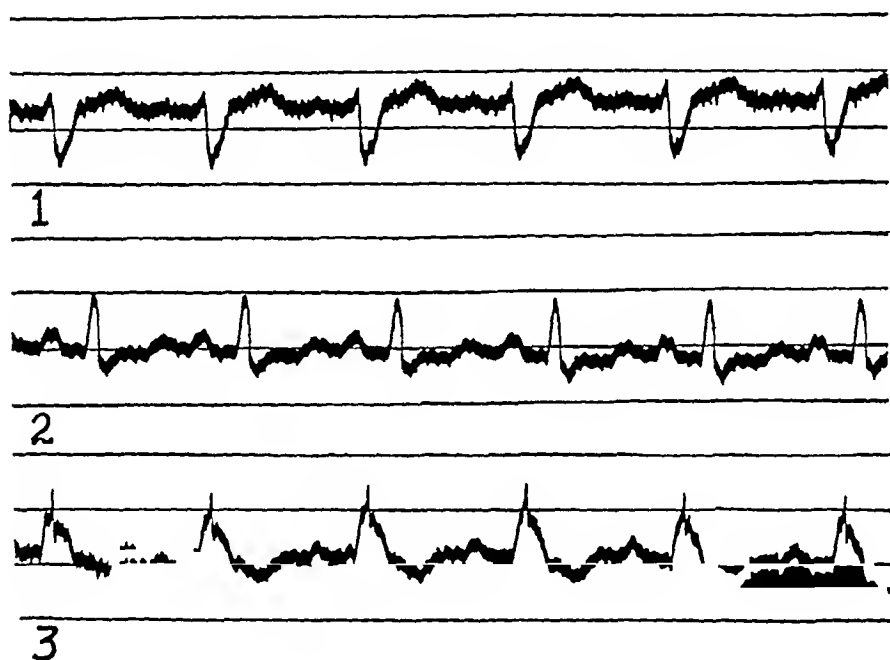


Fig 1 (case 1) —Right bundle branch block The QRS interval was 0.125 second

T waves were not directed oppositely to all the main ventricular complexes, however, except in the last record (fig 1) The PR interval was 0.162 second The electrocardiogram made on Nov 27, 1934, showed also an interpolated extrasystole preceded by the P wave and a shortened PR interval, the main initial ventricular complex was upright in lead I and down in lead III, with the T wave directed oppositely The QRS complex was broad and slurred A solitary QRS complex in lead I was of normal width and form and was preceded by a normal P wave with the same PR interval as in the majority of the QRS complexes, it was followed by an inverted T wave, in contradistinction to the QRS complexes elsewhere in the record, which were followed by positive T waves

Necropsy (performed by Dr Earl R Lundeberg) —Necropsy was performed on the embalmed body the third day after death The following anatomic diagnoses were recorded after a thorough examination acutely perforated duodenal

ulcer, generalized peritonitis, severe cloudy swelling of the kidneys, acute septic lymphadenitis of the abdominal nodes, follicular hyperplasia of the spleen, fibrosis and cloudy swelling of the liver, cardiac hypertrophy (heart unopened at the time), congestion of the lungs, liver and kidneys, moderate atherosclerosis of the aorta, with moderate dilatation, calcification of the iliac arteries, cholelithiasis, chronic fibrous cholecystitis, slight apical pulmonary emphysema, a calcified tubercle in the right lung, simple cysts of the kidneys, an accessory spleen, bilateral arcus senilis, slight senile atrophy of the cerebral cortex, multiple ulcerations of the skin, and emaciation

Gross Examination of the Heart The heart weighed 400 Gm. There was no pericarditis. The left auricle was moderately dilated but not hypertrophied. The mitral valve showed a moderate degree of healed valvulitis, mainly at its free edge and especially on the aortic leaflet, which was considerably thickened at its edge and had one definitely thickened and other slightly thickened chordae tendineae. There was little stenosis, the effect of the lesion having been mainly regurgitation. The left ventricle was slightly hypertrophied. The aortic valve was apparently normal, and the root of the aorta was only moderately atheromatous. The right auricle was moderately dilated. The tricuspid valve was apparently normal. The right ventricle was moderately hypertrophied and dilated. The pulmonary valve appeared normal. The endocardium and myocardium throughout appeared normal. The coronary arteries were considerably dilated throughout and only moderately atheromatous.

Histopathologic Examination of the Heart Four blocks were removed from the auriculoventricular and interventricular septums, which included practically all the microscopically recognizable portion of the conduction system. Block 1 included the entire thickness of these septums and contained the auriculoventricular node and bundle and the origins of the bundle branches. Serial sections were made vertically from behind forward so that the conduction system could be followed progressively from its origin. Block 2 included a long section of the right side of the interventricular septum and contained most of the right bundle branch. Blocks 3 and 4 included between them all the left side of the interventricular septum and therefore most of the left bundle branch. Blocks 2, 3 and 4 were cut serially from above down in the horizontal plane. All blocks were embedded in paraffin, and the serial sections were 10 microns thick. All sections were mounted and kept, but only every tenth one was stained, except in certain areas where others were also stained. Masson's trichrome stain was used mainly. Block 1 was cut into 2,490 sections, block 2 into 2,480 sections and block 3 into 1,500 sections. Only part of block 4 was cut, since it stained poorly.

The auricular myocardium was moderately fibrotic, the blood vessels throughout were greatly dilated, as they were elsewhere in the heart. The arteries showed little sclerosis. The auriculoventricular node was fibrosed in its first portion to the extent of about 50 per cent by an increase in interstitial connective tissue. As it reached its greatest diameter, this fibrosis decreased, and the node became almost normal. The artery to the node was large and dilated and had several branches. Because of the dilatation the course of the arteries was easily followed. Adjacent to the central fibrous body, nearer its left side, there was a large area of fatty replacement of the auricular myocardium. The bundle of His was moderately fibrotic in its inferior half. Toward its end it became even more fibrosed, being replaced about 50 per cent by fibrous tissue. The endocardium on the left side of the interventricular septum was somewhat thickened. The left bundle branch in its upper part contained dense fibrous tissue among its fibers.

but these were apparently not badly damaged. Subjacent to the branch in its upper part there was replacement of the peripheral portion of the myocardium by dense fibrous tissue. As far down as the left bundle branch was traced it contained more than the normal amount of interstitial connective tissue. The bundle of His continued as usual into the right bundle branch. The first portion of this branch was densely fibrosed. In its beginning it was cut longitudinally and was

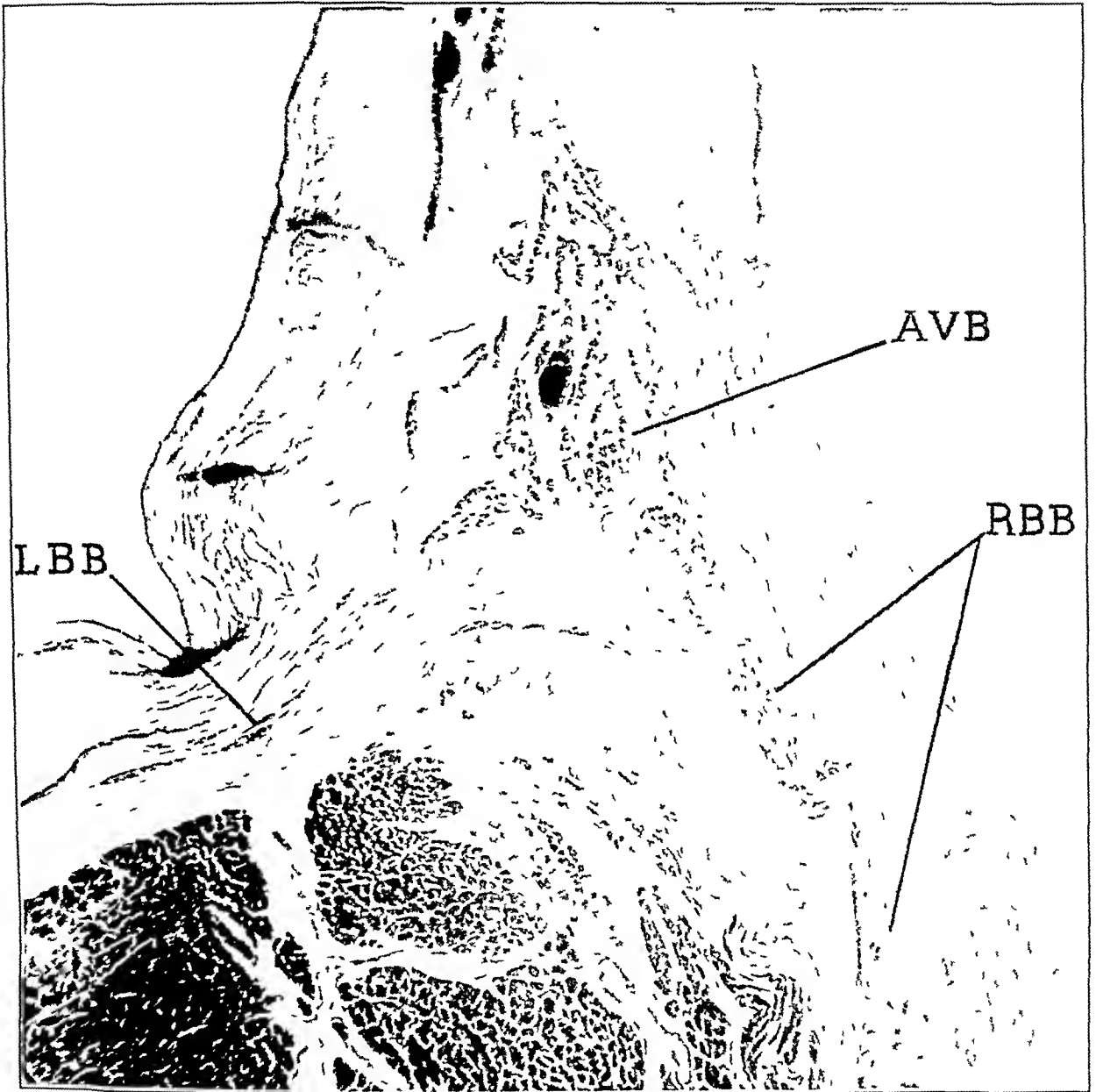


Fig 2 (case 1) —Section 1,580, block 1, showing in vertical cross-section the moderately fibrotic auriculoventricular bundle (*AVB*), the moderately fibrotic left bundle branch (*LBB*) and the densely fibrotic right bundle branch (*RBB*), $\times 75$

mainly a mass of hyaline fibrous tissue, with a few conduction fibers embedded therein (fig 2). The peripheral portion of the myocardium subjacent to the right bundle branch was almost entirely replaced by dense fibrous tissue. As the branch descended in its first few millimeters this area of myocardial fibrosis widened out into a solid scar, several millimeters in diameter, in which the right

bundle branch became embedded and completely lost its identity (fig 3). Large irregular endothelium-lined spaces were present in the peripheral portions of the scar. After having vanished in the scar for about 3 mm of its myocardial portion (the middle portion of the branch), the right bundle branch was seen gradually emerging from the lower peripheral portion of the scar (fig 4). The branch



Fig 3 (case 1)—Section 470, block 2, showing the dense, solid scar in the interventricular septum in which the right bundle branch has become completely destroyed, $\times 117$

gradually assumed a more nearly normal appearance and gradually approached the slightly thickened endocardium, where it spread out in its usual way. Throughout this part of its course it contained a little more than the normal amount of interstitial connective tissue. The upper half of the interventricular septum, par-

ticularly the myocardium, in general, contained a little more than the normal amount of connective tissue between the muscle fibers. Most of the muscle fibers were somewhat shriveled, owing probably to long fixation in solution of formaldehyde. There were also a few small scars in the myocardium besides the



Fig 4 (case 1)—Section 850, block 2, showing in cross-section the right bundle branch (*RBB*) gradually emerging from the lower peripheral portion of the scar shown in figure 3, $\times 263$

main one already described. The vessels throughout were dilated and thin walled, and endothelium-lined blood spaces of various sizes and shapes were numerous. In a few areas there was discrete diapedesis of erythrocytes. Many

of the arteries, especially the larger ones, were surrounded by more than the normal amount of connective tissue. The capillaries and arterioles in the bundle branches were often intensely engorged. The tricuspid valve as it appeared in the sections was essentially normal.

Summary—A man aged 50 years presented evidence of heart disease for more than a year before his death, but the etiologic factor thereof was not clear. Shortly before death occurred the liver became engorged, but there was little edema detectable otherwise. Electrocardiograms showed "right bundle branch block," which was not complete, however, until just before death. General peritonitis, the result of acute perforation of a chronic duodenal ulcer, hastened death. The heart was moderately enlarged. The mitral valve showed healed valvulitis which had produced regurgitation but not much stenosis. The coronary arteries were all dilated and thin walled. Serial sections of the conduction system showed some fibrosis of the auriculoventricular node and bundle. The left bundle branch contained definitely more than the normal amount of interstitial connective tissue throughout. The first portion of the right bundle branch was very fibrotic, and in a short part of its intramyocardial course it was completely destroyed by involvement in a dense peripheral myocardial scar. The remainder of the branch was relatively normal. The myocardium in general was somewhat fibrotic and contained a few small definite scars.

Comment—The pathogenic factor in this case was probably ancient rheumatic arteritis which produced myocardial infarction in the region of the intramyocardial portion of the right bundle branch and destroyed a portion of it. The vascular disease had resulted in thinning and dilatation of the vessels. The only other plausible explanation would be that the myocardial changes resulted from rheumatic myocarditis, but the character of the lesions was much more suggestive of healed infarcts. The small scars were not large enough greatly to compromise the function of the myocardium. The arterial disease, however, had produced malnutrition of the left bundle branch and of the endocardium, with resulting moderate but extensive interstitial fibrosis of the branch. The fibrotic condition of the bundle of His was not severe enough to produce impairment of auriculoventricular conduction. The bundle branch block was certainly of many years' standing, since the lesions all indicated great age, but there was no history of the time of onset of the rheumatic infection. The electrocardiogram did not show the large voltage originally described for bundle branch block, but it fulfilled the original criteria in other respects. Speculation would be interesting but inconclusive in regard to the cause of the single QRS complex of normal form referred to.

CASE 2¹⁶⁵ (Army Medical Museum accession no. 50187) —*Clinical Record*—Mrs. E. M., a housewife aged 46 years, was admitted to the Torbett Sanatorium and Diagnostic Clinic, Marlin, Texas, on March 26, 1936, complaining of shortness of breath, flutter and palpitation of the heart, pain in the chest and swelling of the

¹⁶⁵ Dr. J. Walter Torbett Jr., of the Torbett Sanatorium, gave me permission to use the records of this case and to study the heart.

feet and legs She had typhoid in childhood and many typical attacks of inflammatory rheumatism between the ages of 8 and 33 years She had an operation for gallstones fifteen years before entry Dyspnea on exertion and precordial pain had first been noted nine years before entry, but she had not consulted a physician These symptoms did not become severe until four years before entry, when more dyspnea, wheezing and rattling noises in the chest and a sense of oppression or dull aching in the chest and neck developed She attributed these symptoms to obesity, attempted to reduce and went to bed for a while, still without consulting a physician Attacks of "asthma" lasting three to four weeks then began to occur about twice a year She improved somewhat, but one and a half years before she was admitted to the hospital her heart began to "flutter and skip and beat fast," and there was considerable pain in the chest A physician then told her that she had an enlarged heart, with leakage and irregular action Six months before admission to the hospital she began to have orthopnea, with severe coughing at the onset, and two months before entry, edema appeared in the feet and gradually ascended to the waist Recently she had coughed up frothy pink material She had not taken any medicine for her heart

Physical examination revealed an obese orthopneic woman, with cyanosis of the ears, fingers, toes and lips The veins of the neck were greatly distended The arterioles of the retinas showed moderate tortuosity and some arteriovenous compression, and the margins of the optic disks were slightly blurred There were impaired resonance, with some diminution of intensity of the breath sounds, and moist rales at the bases of the lungs The apex beat was diffuse, and the exact size of the heart could not be determined The heart sounds were muffled and distant The cardiac rhythm was totally irregular, and the rate was about 100 per minute A distant to and fro murmur heard over the apex and along the left sternal border was thought to be that of mitral stenosis The radial pulse was almost imperceptible The blood pressure was determined with difficulty and was about 110 systolic and 40 diastolic There was marked pitting edema of the lower extremities, the abdomen and the back The edge of the liver could not be felt because of the obesity and edema The temperature was normal The urine contained albumin, grade 2 A hemogram and the blood urea were normal Wassermann and Kahn tests of the blood gave a negative reaction

Electrocardiograms showed typical right bundle branch block, auricular fibrillation and an occasional ventricular extrasystole (fig 5) The rate varied from 110 to 120 per minute according to the number of premature beats The amplitude was not appreciably increased The QRS interval was 0.12 second Definite notching was present in lead II There was slight variation in the configuration of the complexes Electrocardiograms on two consecutive days showed the T wave broader and rounder and the heart rate considerably slower on the second day

The patient was given the usual treatment for congestive failure, although there were some diuresis and slowing of the heart rate to 70 per minute She died on April 2, seven days after admission to the hospital

Necropsy—Permission for necropsy included only study of the chest The heart was removed three hours after death and placed in solution of formaldehyde U S P diluted 1:10

Gross Examination of the Heart The heart weighed 560 Gm The two layers of the pericardium were almost completely adherent because of old fibrous adhesions The large coronary arteries were relatively little affected by any degenerative process The aorta showed practically no atherosclerosis The left auricle was hypertrophied and dilated, grade 2 There were two smooth, fibrous plaques, about 1.5 cm in diameter, in the endocardium of the posterior wall The

mitral valve was densely fibrotic and largely calcified, and there was stenosis, grade 4, of the auriculoventricular orifice. The chordae tendineae were moderately thickened and greatly shortened. The cavity of the left ventricle was relatively small. The wall was 2.3 cm thick in its upper third. The aortic valve was moderately fibrotic, and its two anterior cusps were fused. There had evidently been a little stenosis and regurgitation. The membranous portion of the interventricular septum was thickened and fibrotic. In the left ventricle just below the junction of the membranous and muscular portions of the septum there was a circular fibrous plaque, about 1 cm in diameter, directly in the track of the first part of the left bundle branch (fig 6). It had a thick, elevated, rounded rim and a depressed center. The remainder of the endocardium of the left ventricle appeared normal except for an area below the plaque, where it was a little thickened and white. There were some small patches of white fibrous tissue in the myocardium and some thin fibrous linear areas. The right auricle was hypertrophied and dilated like the left. The tricuspid valve showed fibrous



Fig 5 (case 2) —Auricular fibrillation and right bundle branch block, with a QRS interval of 0.12 second and a ventricular premature contraction

scarring, with fusion between the septal and the anterior leaflet, but the function of the valve apparently had not been much altered. The valve at the area of scarring was considerably thickened just at the point where the right bundle branch arises, and for some distance below that the endocardium was apparently thickened. The right ventricle was not much dilated. Its wall was 0.75 cm thick in its upper third. The pulmonary valve appeared normal, and the pulmonary artery was smooth.

Histopathologic Examination of the Heart Three blocks were removed from the heart which included the lower part of the auriculoventricular septum and the major portion of the interventricular septum. All 3 included the entire thickness of the septums. Blocks 1 and 2 contained the greater portion of the conduction system. Block 1 contained the auriculoventricular node and bundle and the origins of the bundle branches. Serial sections were made vertically from behind forward so that the conduction system could be followed progressively from its origin. Block 2 included the upper two thirds of the interventricular septum and contained the major portion of the two bundle branches. This block was cut serially from

above down in the horizontal plane. Block 3 was embedded in paraffin but was not cut, since the important lesions were found to be in block 2 and only a small portion of the two branches remained in block 3. Blocks 1 and 2 were embedded in paraffin, and the serial sections were 10 microns thick. All sections were mounted, but only every tenth one was stained. Masson's trichrome stain was used. All sections were numbered and kept permanently. Block 1 was cut into 2,080 sections and block 2 into 1,820 sections.



Fig 6 (case 2) —The opened left ventricle, showing the left side of the inter-ventricular septum with the circular fibrous plaque (S) just below the aortic valve in the track of the first part of the left bundle branch

The auricular myocardium in block 1 was considerably degenerated. There was a moderate increase in the amount of interstitial fibrous connective tissue, and many of the myocardial fibers showed degeneration mainly in the nature of edema, giving a vacuolated appearance. The myofibrils were distinctly separated and no longer parallel. Many of the fibers appeared to be no more than empty tubes with a thin membranous wall. The cross-striations were indistinct and

granular In some areas the auricular myocardium presented a fibrotic, gnarled appearance The exocardium was greatly thickened owing to fibrosis The myocardium of the upper portion of the interventricular septum contained in this block was moderately fibrotic There was not as much degeneration of the myocardial fibers as in some parts of block 2



Fig 7 (case 2) —An arteriole of the interventricular septum, showing subintimal proliferation, scarring of the media and a thrombus in the lumen attached to the intima by thin strands of fibrin, $\times 289$

Practically all the arteries and arterioles throughout all the sections showed definite evidence of healed rheumatic arteritis In many instances these changes affected all the coats of the vessels One of the commonest changes, especially in the smaller vessels, was subintimal fibroblastic proliferation and edema (fig 7) The media was also often edematous and contained pale collagenous tissue, with

the muscle fibers reduced in number, separated and often arranged in patches (fig 8) The walls of the arteries, especially of the larger ones, were irregularly thickened, and the lumens were irregularly narrowed Sometimes one side of the wall was thin and the other thick and markedly degenerated An occasional arteriole was completely occluded by fibroblasts (fig 8C) The adventitia and surrounding fascia often contained an excess of fibrous tissue Many of the smaller arteries and arterioles contained relatively fresh thrombi in the center of their lumens, with thin strands of fibrin passing between the intima and the thrombus The vessels seemed to be present in increased numbers, especially about the periphery of and within the central fibrous body The vessels within the elements of the conduction system were affected similarly to those elsewhere, but the capillaries were often more distended, giving the appearance of intense congestion

The auriculoventricular node was degenerated in much the same way as the auricular myocardium and contained somewhat more than the normal amount of connective tissue Both the auriculoventricular node and the first half of the bundle contained some relatively large empty spaces, possibly dilated lymph channels The bundle of His appeared to be more nearly normal than the node and contained only a slight excess of connective tissue The fibers were cut transversely, as they are in the technic employed, and the myofibrils stood out prominently, giving a granular appearance to the fibers The first portion of the left bundle branch seen, the upper posterior part, was relatively normal, lying under a slightly thickened endocardium As the raised endocardial scar on the left side of the septum was approached, the branch passed down under its base and was embedded in fibrous tissue (fig 9) It became thinner, and its fibers were often more separated The fibers varied in size, many being broader than normal and presenting a vacuolated appearance The branch seemed to have considerable difficulty in passing beneath the middle and anterior portions of the scar, being thin, but nowhere was it completely interrupted The raised endocardial scar was thick and was composed of dense fibrous tissue, with a sprinkling of nuclei In its base there were large irregular endothelium-lined spaces containing blood The root and proximal portion of the septal leaflet of the tricuspid valve was thick, fibrous and vascular Toward its end the bundle of His contained a little more fibrous tissue than in its main extent It terminated in the usual way as the right bundle branch The first part of this branch appeared fairly normal, but as it approached the endocardium it became progressively fibrotic, until about half of it was replaced by fibrous tissue Beyond this point in block 1 the amount of fibrous tissue slowly decreased to about 25 per cent of the substance of the branch, but the branch was passing into an area of severe fibrosis beneath the endocardium near the base of the tricuspid valve The mitral and aortic valves were thick, fibrous and vascular

In block 2 the bundle branches were cut transversely The first portion of the right bundle branch seen was fairly normal, but it rapidly became fibrotic as it lay just beneath the attachment of a markedly fibrotic chorda tendineae which had its roots in a dense scar in the myocardium This bundle branch finally became so replaced by hyaline fibrous tissue that only one or two thin muscle fibers remained embedded in the scar (fig 10) One or two small blood vessels remained in it This situation maintained for some little distance (from section 260 to section 460), but then the fibrosis gradually decreased until in the third, or lower, subendocardial portion of the branch it consisted of only about 10 per cent of fibrous tissue between the muscle fibers It was no longer embedded in the myocardial scar The left bundle branch continued downward uninterruptedly in the



Fig 8 (case 2) —Three arterioles in the interventricular septum, showing in *A* one with a very fibrous and distorted media, in *B* one with marked edema of the media and a narrowed lumen, and in *C* one completely occluded by fibroblasts, $\times 361$

subendocardial areolar tissue of the left side of the septum, but it was not normal. Its fibers were variable in diameter, the larger ones looked like vacuoles, and there was considerable fibrous tissue among the fibers. The lower part of the raised endocardial scar was present for some distance, beneath which the branch was most affected (fig 11). The branch spread out beneath the otherwise fairly normal endocardium as usual, but a definite division into anterior and posterior divisions was not apparent (as is not infrequently the case in the human heart). The branch was followed into the bases of the papillary muscles, mainly, however, the anterior, where the fibers were large, close together, pale and almost normal.

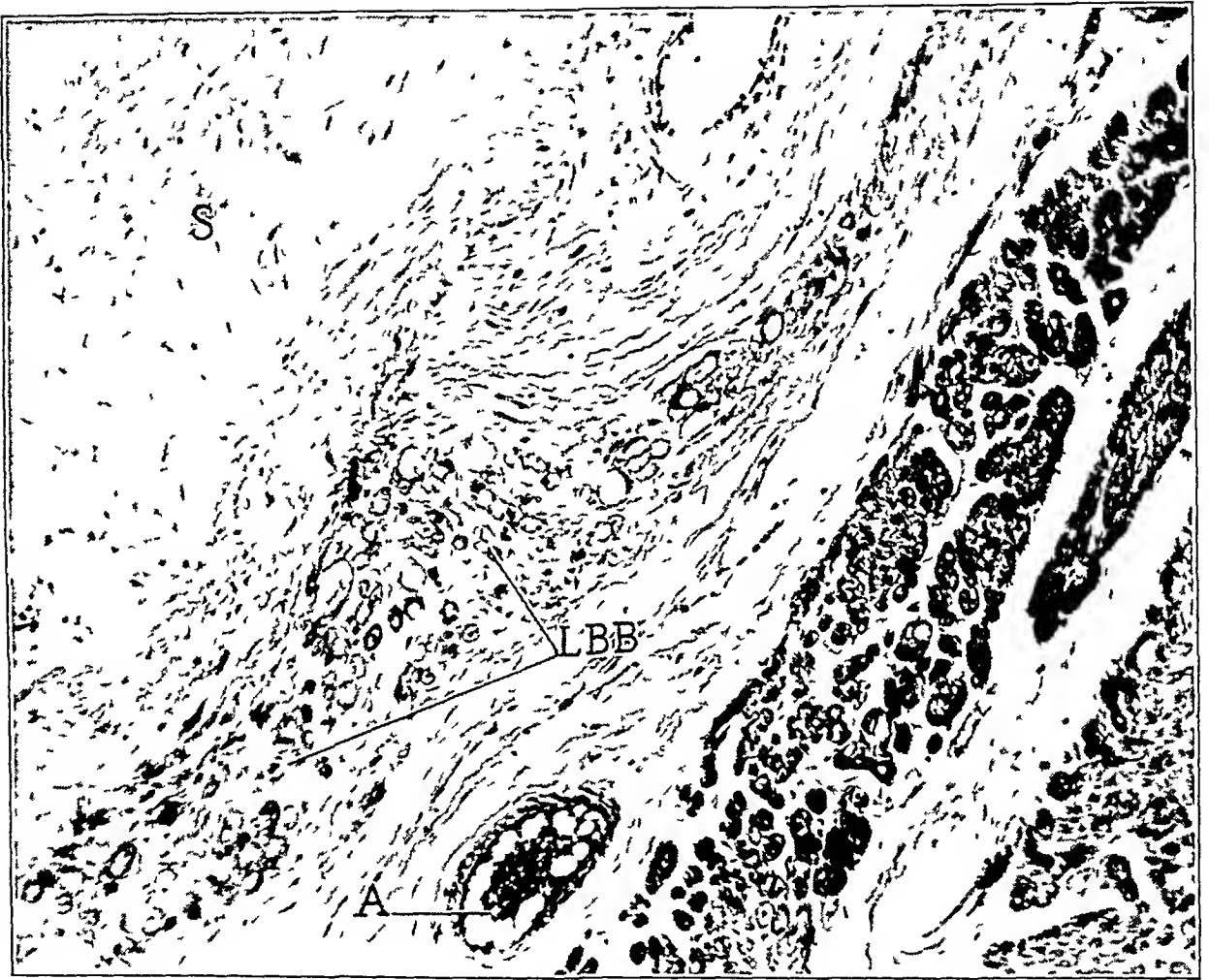


Fig 9 (case 2) —Section 1,060, block 1 ($\times 133$), showing the upper portion of the left bundle branch (*LBB*) passing between the myocardium and the endocardial scar (*S*) pictured in figure 6. An arteriole is shown (at *A*) similar to the one pictured in figure 7.

The passage into the base of the posterior papillary muscle was not so easy to follow, because the fibers were smaller and more separated. The myocardium of the interventricular septum in block 2 was considerably degenerated in many areas. Except for the scar in the region of the middle portion of the right bundle branch, there was only a moderate increase in interstitial connective tissue, but there were many foci in which there was considerable edema of the myocardium and what appeared much like liquefaction necrosis.

Summary—A woman, aged 46 years at the time of death, had had frequent attacks of rheumatic fever since the age of 8 years. For nine years she had had symptoms suggestive of heart disease, and for more than six months there had been symptoms of severe congestive failure. Electrocardiograms made a few days

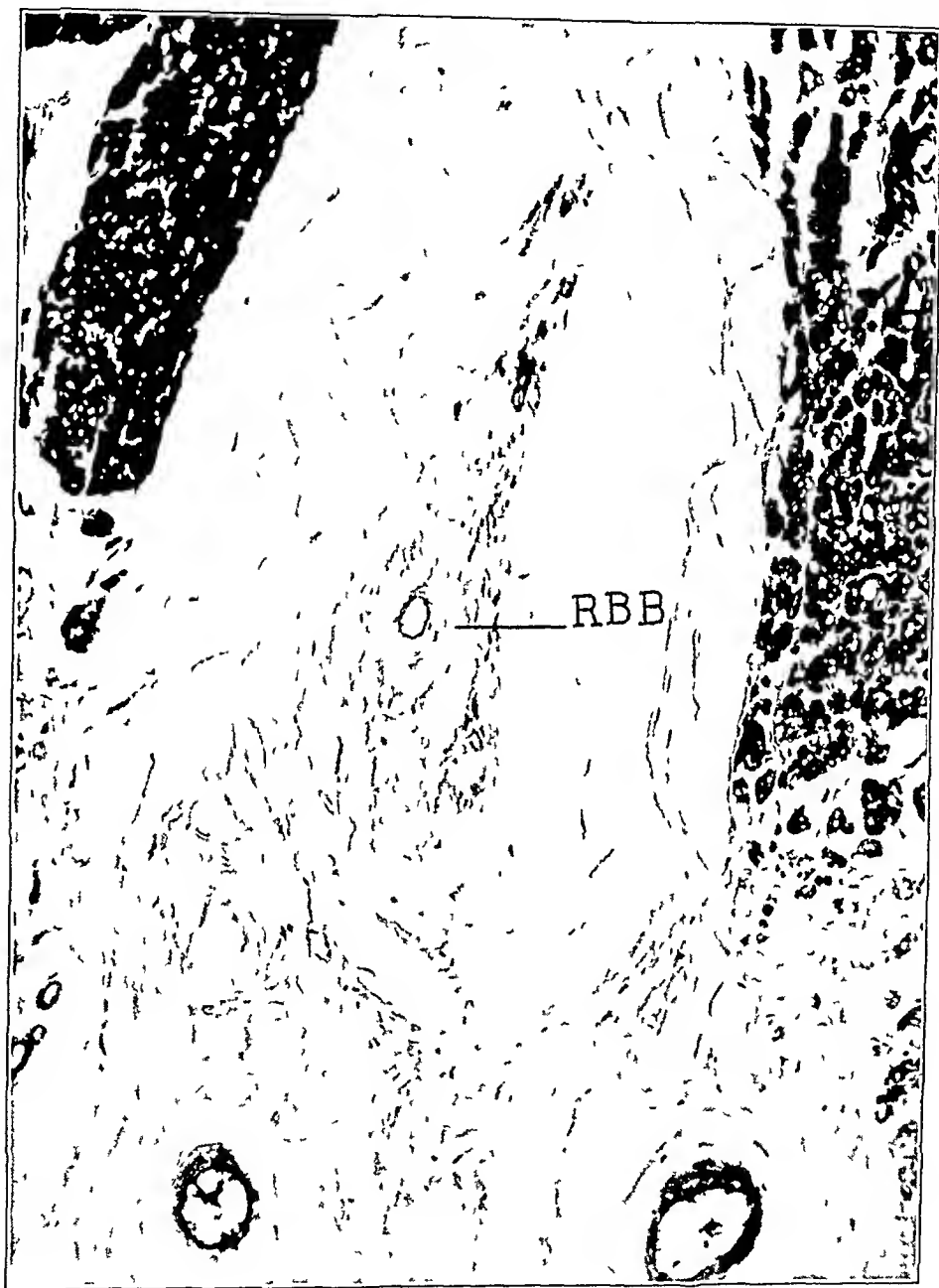


Fig 10 (case 2) —Section 260, block 2, showing in cross-section the right bundle branch (*RBB*) almost completely replaced by hyaline fibrous tissue, $\times 137$

before death showed right bundle branch block, auricular fibrillation and extrasystoles. The heart showed severe mitral stenosis and moderate scarring of the aortic and tricuspid valves. There was a raised endocardial scar in the upper part of the left side of the interventricular septum. The myocardium showed micro-

scopically patchy degeneration and healed rheumatic arteritis. Serial sections through the conduction system showed that the auriculoventricular node and bundle were only slightly degenerated, but there was practically complete replacement of the right bundle branch by hyaline fibrous tissue in part of its intramyocardial portion as it entered a scar in the peripheral part of the myocardium. The left bundle branch was not normal, particularly as it passed beneath the raised endocardial scar, but it was not interrupted in any portion. Many of its fibers were swollen and embedded loosely in fibrous connective tissue.

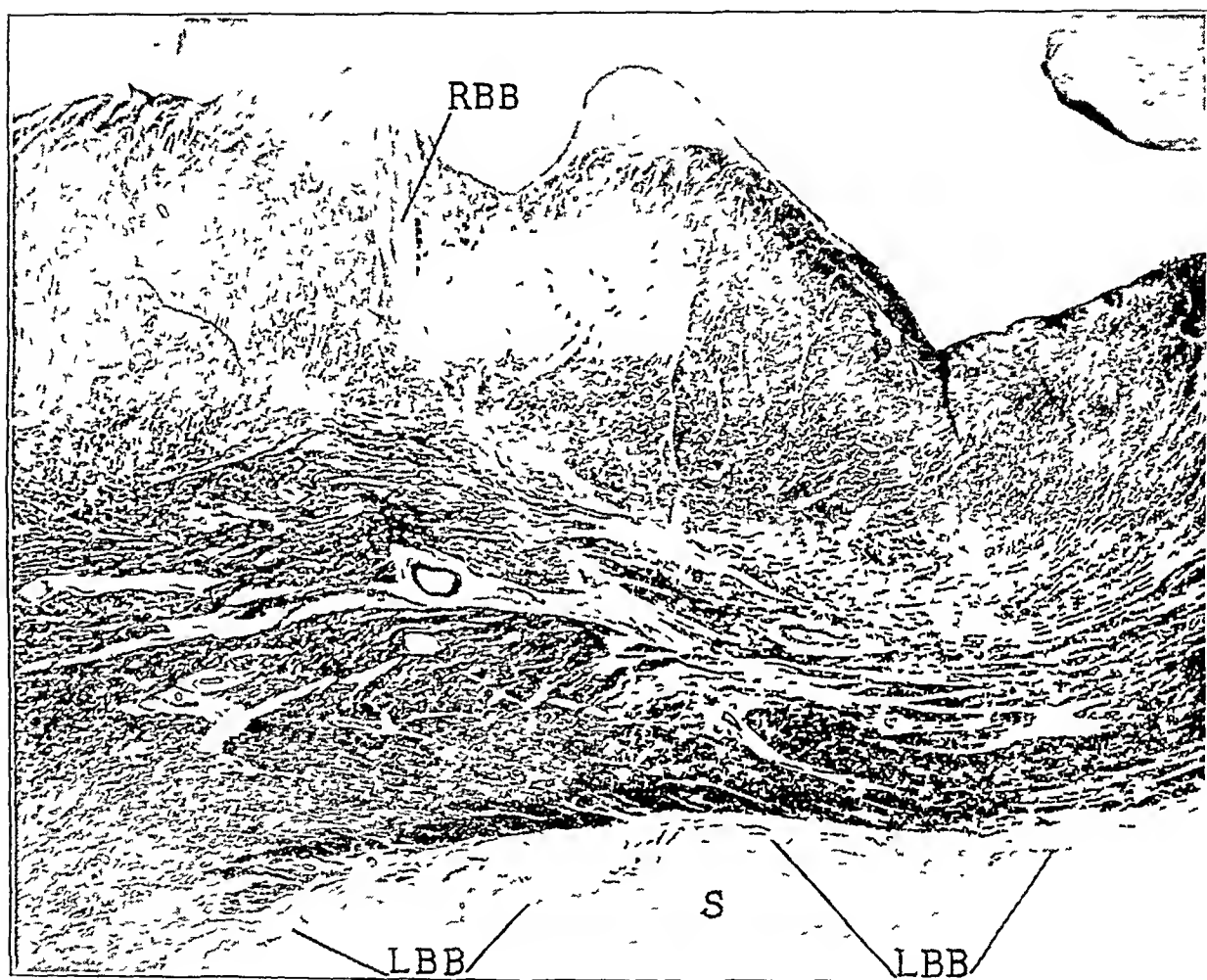


Fig 11 (case 2) —Section 220, block 2, showing the interventricular septum in cross-section, with the fibrotic right bundle branch (*RBB*) near the right side (top) and the compromised left bundle branch on the left side (bottom), $\times 10$

Comment—The pathogenesis of the myocardial degeneration and the main lesions of the bundle branches was undoubtedly due to old rheumatic arteritis, although the endocardial scar in the left ventricle which comprised the left branch was probably due to endocarditis. The arterial disease was extensive and affected only the small arteries and arterioles. Similar vascular lesions due to rheumatic infection have

been described by Kaisner and Bayless¹⁶⁶ (1934), by Gross, Kugel and Epstein¹⁶⁷ (1935), and by others. There was no doubt as to the bundle branch more seriously affected. It is unbelievable that the right branch could conduct at all.

The case illustrates well the point that it is impossible usually from a gross examination of the heart to state which bundle branch is destroyed. The endocardial scar lying in the track of the beginning of the left branch could readily have been considered adequate to cause destruction of that branch, but extensive histologic study showed the branch probably to be capable of functioning, whereas the right branch, unassociated with any indictable gross lesion, was almost totally destroyed in part of its course. As in case 1, the amplitude of the ventricular complex was not great.

CASE 3¹⁶⁸ (Army Medical Museum accession no 44641) —*Clinical Record*— A young man, aged 24 years at the time of his death, on Nov 1, 1934, had never been seriously ill until shortly before that time. He had never had rheumatic fever but had had some mild attacks of sore throat. Five years before his final illness he had a cough for a short time, and a cardiac murmur had been discovered and attributed to chronic tonsillitis. He had engaged in athletics without difficulty, but after this illness he abandoned strenuous sports, although he continued to work and study hard. In May 1934 he suddenly fainted but recovered quickly and felt as usual thereafter. On August 21, however, after a busy and exciting period of preparation for marriage, he awoke feeling bad and somewhat dyspneic on exertion. Examination at this time revealed a tall, slender young man who did not appear ill. The examination revealed no abnormality except moderate enlargement of the heart, the dullness extending about 10 cm to the left of the midsternal line in the fifth intercostal space, and a loud high-pitched systolic precordial murmur. The pulse rate was 80 per minute and regular, and the blood pressure was 100 systolic and 70 diastolic. The patient was reassured, and he resumed his usual activities without further symptoms. On September 26 he had a second short fainting spell during a busy evening. On the following day he had several short attacks of syncope. His pulse was found to vary in rate and strength, being slow and strong during the attacks and more rapid and weak between them. The use of ephedrine had a beneficial effect.

The first electrocardiogram was made on this day (fig 12). It showed sinus rhythm at the time, with a rate of 80 per minute. The PR interval measured 0.16 second and the QRS complex 0.16 second in all three leads. The main ventricular complex was down in lead I and upright in leads II and III. It was notched in lead I and severely slurred in leads II and III. In the latter leads the amplitude was 20 and 22 mm, respectively. The T wave was upright in lead I and deeply inverted in leads II and III, in which it passed almost directly downward from the descending limb of the R wave.

166 Kaisner, H. T., and Bayless, F. Coronary Arteries in Rheumatic Fever, *Am Heart J* 9 557, 1934.

167 Gross, L., Kugel, M. A., and Epstein, E. Z. Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, *Am J Path* 11 253, 1935.

168 Dr Benjamin F. Weems had charge of the patient and gave me permission to study the heart and report the case.

From this time on the patient suffered almost daily from these brief attacks of syncope. It became apparent that there were varying degrees of heart block, with short periods of asystole, in which the patient became pale and unconscious. During these periods the auricular pulse could be observed in the veins of the neck. In some attacks there were as many as 125 auricular contractions without a single ventricular beat. Electrocardiograms made on October 2 verified these findings (fig 13). The general characteristics of the complexes were the same as in the first tracing. The auricular rate throughout the periods of block was rapid, usually about 140 per minute, and it was more rapid the greater the degree of auriculoventricular block. During the phases of sinus rhythm the rate was about 80 per minute. The P wave was notched and tall during the periods of block, measuring as much as 5 mm. The PR interval varied with different periods

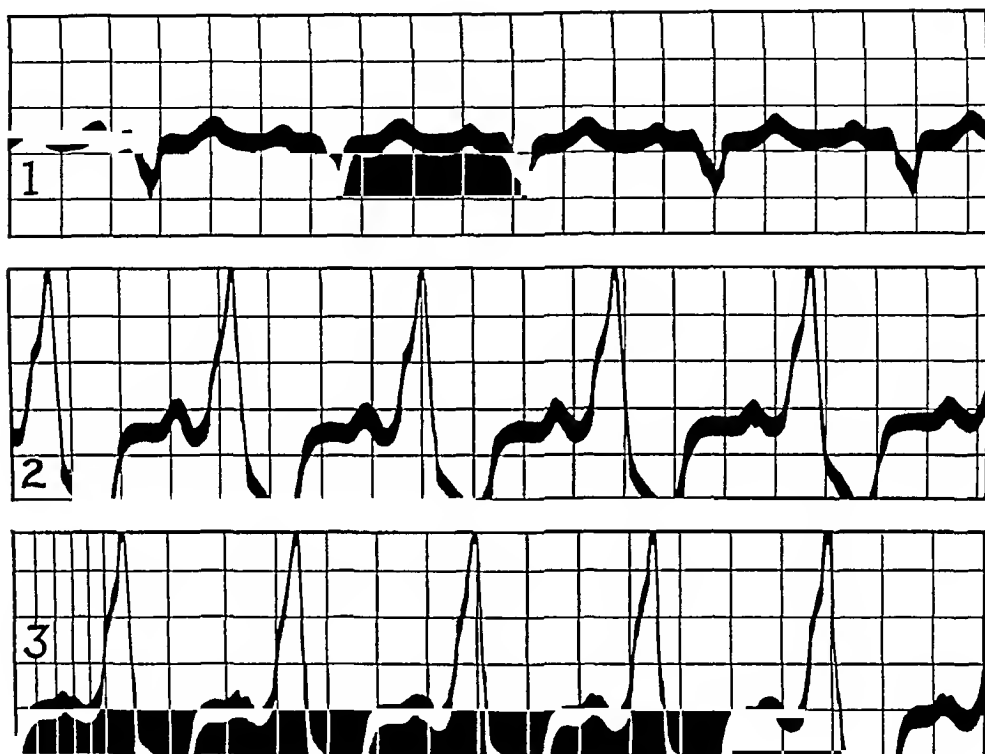


Fig 12 (case 3)—Right bundle branch block with large amplitude in leads II and III and a QRS interval of 0.16 second

of block. A striking point was the fact that neither in this nor in subsequent electrocardiograms were there any periods of idioventricular rhythm and that Wenckebach periods were never noted. The amplitude of the waves in leads II and III was greater than it was in the first tracing, the R wave being 38 mm high. Electrocardiograms made on two subsequent occasions were similar.

During one attack of unconsciousness, on October 4, the patient became opisthotonic and ceased to breathe. Injections of solution of epinephrine apparently restored him. Nausea and vomiting developed and became very troublesome. Vomiting appeared to precipitate many of the attacks of unconsciousness. In spite of the frequent administration of ephedrine, the syncopal attacks continued to occur many times daily. Epinephrine was injected from time to time. Digitalization was attempted with the idea of producing permanent complete heart block and stabilizing the cardiac action, but vomiting precluded the oral administration of

the drug, and it was discontinued after a few doses. A few days later digifolme was given intravenously. The pulse rate became 32 per minute and remained at about this figure for many hours at a time, during which the syncopal attacks were much less frequent. The patient repeatedly complained of gastric and intestinal flatulence and paroxysms of pain of a crampy nature in the lower portion of the abdomen. The ephedrine used was held to be at least partly responsible for much of the gastro-intestinal disturbance, and the dosage was reduced. However, there was little amelioration, and the patient died in an Adams-Stokes attack during the night, less than six months after his first syncopal attack and a little more than

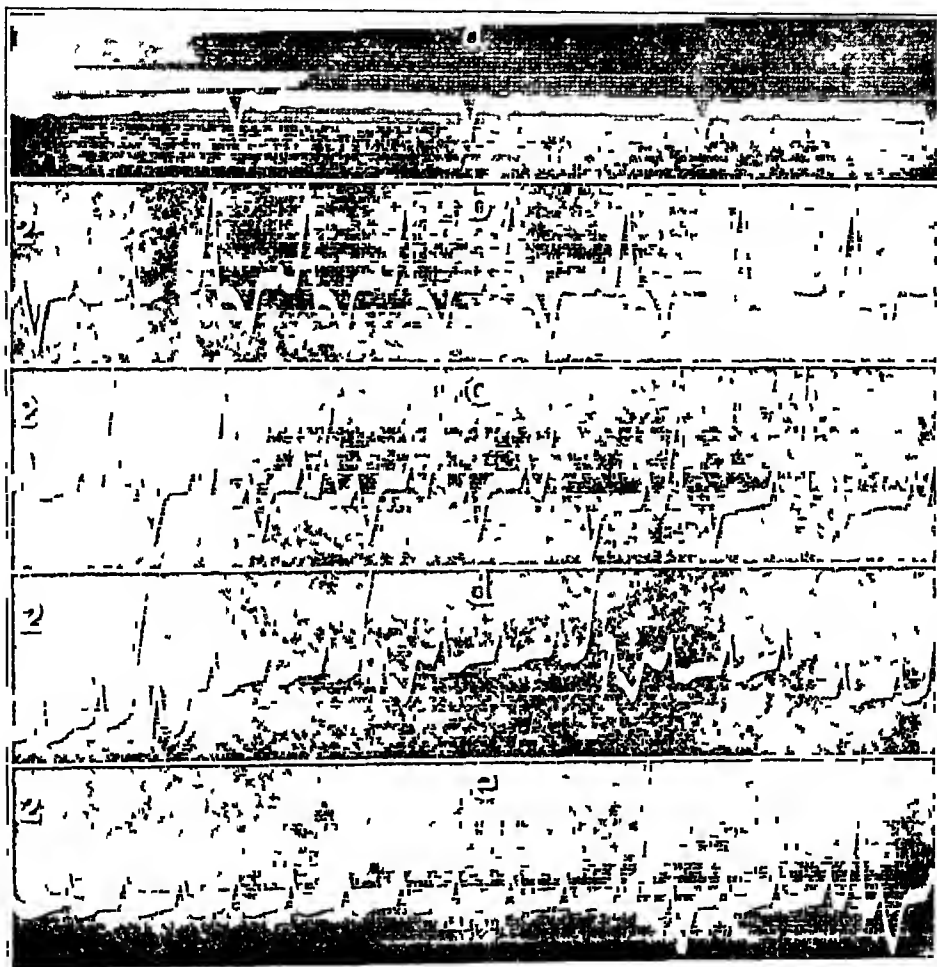


Fig 13 (case 3) —Composite reproduction of sections of several electrocardiograms, all sections except the uppermost showing lead II *a*, (lead I) there is four to one heart block, *b*, most of the tracing shows sinus rhythm, *c* two to one heart block, *d*, four to one heart block, *e*, a long period of asystole (only partly shown) is followed by a period of four to one block. In *c*, *d* and *e* the P wave is tall and notched. The PR interval varies. A large amplitude is shown in all tracings of lead II.

a month after the attacks became frequent. At no time had there been any evidence of an active inflammatory process. The patient remained at home, and few laboratory tests were performed.

Necropsy—Necropsy was performed by Dr Weems less than three hours after the patient died. There was essentially no abnormality except for emaciation and old fibrous adhesions to the upper lobe of the left lung. There was no evidence of passive congestion.

Gross Examination of the Heart The heart weighed 450 Gm. The pericardium had a generally milky tinge. On the lateral surface of the left ventricle near the base and apex and also near the base of the right ventricle posteriorly, there were a few subepicardial hemorrhages, about 0.5 cm in diameter. The chambers were not dilated, but they were all hypertrophied, especially the left auricle and the right ventricle. The former was about 0.5 cm and the latter 0.8 cm thick. The average thickness of the left ventricle was 1.5 cm. The interventricular septum was very thick, about 3 cm, and grossly showed much scarring. All the valves

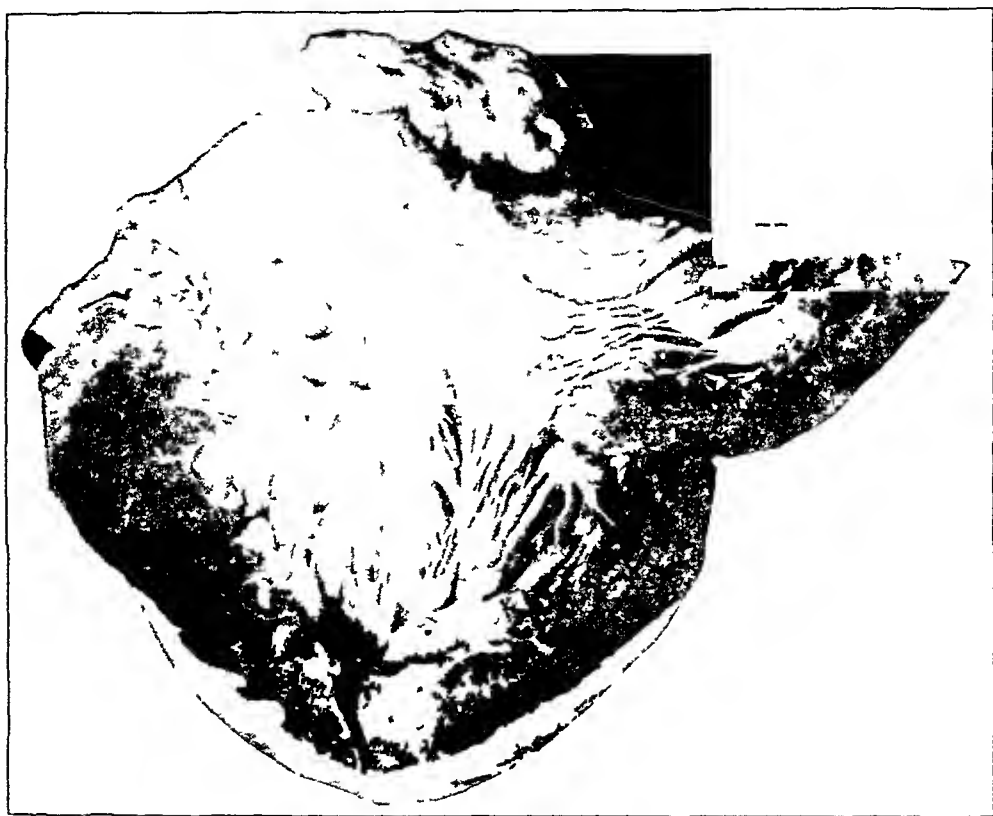


Fig. 14 (case 3)—The opened left ventricle, showing hypertrophy of this ventricle and whitish thickening of the interventricular septum, especially in the upper portion.

appeared normal. The measurements of the valvular orifices were as follows: aortic, 6 cm; mitral, 8.5 cm; pulmonic, 6.5 cm; tricuspid, 9 cm. There were a few streaks of white in the myocardium in general. The endocardium of the left ventricle over the membranous portion and the upper part of the muscular portion of the interventricular septum for about 3 cm below the aortic valve appeared thick and white (fig. 14). A similar appearance was noted on the ventricular endocardium beneath the anterior leaf of the mitral valve. Below these areas there was a less notable and more patchy milky appearance of the endocardium over the septum. On the right side of the septum the endocardium presented a moderately milky appearance, but nowhere was this as marked as on the left side. The endocardium of both auricles had a slightly milky appearance. The foramen

ovale was closed. The orifices of the coronary arteries and the vessels themselves appeared normal. There was slight atheroma of the root of the aorta.

Histopathologic Study of the Heart Blocks of tissue were removed from the auriculoventricular and interventricular septums which included practically all the microscopically recognizable portion of the conduction system. Block 1 included the auriculoventricular node and bundle and the origin of the two bundle branches. Serial sections were cut vertically from behind forward after the block had been embedded in paraffin. This block was cut into 1,040 sections of 10 microns thickness, all were mounted, and every tenth section was stained with Masson's trichrome preparation. Block 2 included the greater part of the interventricular septum, which because of its thickness had been cut down the middle in such a way that this block contained the left half of the septum with the endocardium of the left ventricular surface and therefore most of the left bundle branch. There were 1,517 sections made from block 2, all of which were mounted, and every tenth section was stained with Masson's trichrome preparation. Block 3 contained the opposite half of the interventricular septum facing the right ventricle, it therefore contained the right bundle branch. The block was cut into 1,860 sections, many of which were stained with Van Gieson's connective tissue stain and many with Masson's stain, all being mounted. A total of 4,417 sections was made.

The artery of the auriculoventricular node was much thickened, as were many of the arteries in the myocardium (fig 15). The thickening was due not to intimal changes but to fibrosis of the media particularly, so that this coat was fragmented and appeared moth eaten. The thickness of the wall was irregular. The lumen was moderately reduced in diameter. A rim of dense fibrous tissue surrounded many of the arteries. The node was only slightly abnormal, with a small increase in interstitial connective tissue. The auricular myocardium was moderately fibrotic. The auriculoventricular bundle was considerably more fibrotic than the node, about 20 to 25 per cent of its substance being dense interstitial connective tissue in its first half and close to 50 per cent being fibrous tissue in its other half, which lay just below the central fibrous body and nearer the left side of the septum than usual. The origin of the right bundle branch was at least 50 per cent fibrotic, whereas the origin of the left branch was perhaps less so.

The endocardium of the upper third of the left side of the interventricular septum was replaced by dense acellular fibrous tissue, which was 2 mm thick in some parts. Below this it became rapidly thinner and finally of nearly normal thickness. In the upper third of the septum there were a few patches of dense scar tissue. These rapidly became larger and more numerous until the septum was composed almost entirely (at least 80 per cent) of scar tissue. There was no evidence of recent inflammatory reaction. The left bundle branch was represented by only a few fibers in the middle of the septum. These were deep in the thickened endocardium and close to the myocardium in the upper half but were more superficial lower down (fig 16). In the lower half of the septum they were so few and so difficult to distinguish from the myocardial fibers isolated in the scar tissue that one could not be entirely sure there were any left.

The upper endocardial portion of the right bundle branch was only moderately replaced by fibrous tissue (fig 17A), but as the branch penetrated into the myocardium adjacent to a small peripheral scar it rapidly became replaced by fibrous tissue and lost its identity (fig 17B to D). The scar tissue representing the branch could be followed, however, and this finally approached the endocardium, where it became a triangular area of loose connective tissue entirely devoid of Purkinje fibers. There was no question about the complete replacement of the right bundle branch in its lower half.

One section of the lateral wall of the left auricle showed moderate scarring, one from the base of the lateral wall of the left ventricle showed a great deal of fibrous tissue and one from the lateral wall of the right ventricle showed only a moderate amount of scar tissue

Summary—A man aged 24 years was told he had a cardiac murmur five years before he died. Less than six months before he died he had a short attack of



Fig 15 (case 3)—A small artery of the interventricular septum, showing the moth-eaten appearance of the media due to fibrosis and edema, irregular thickening of the wall and moderate reduction in the size of the lumen, $\times 85$

syncope. A little more than a month before he died similar attacks recurred and became more and more frequent. Great variation in the pulse rate was noted, and the syncopal attacks occurred during periods of asystole. Electrocardiograms showed almost classic right bundle branch block and many transitions from sinus

rhythm to different degrees of partial heart block and asystole. They did not show any periods of idioventricular rhythm, however. Death occurred in an Adams-Stokes seizure. The heart was moderately enlarged, its chambers were hypertrophied, especially the left auricle and the right ventricle, but they were not dilated. The valves and large coronary arteries appeared normal. The endo-

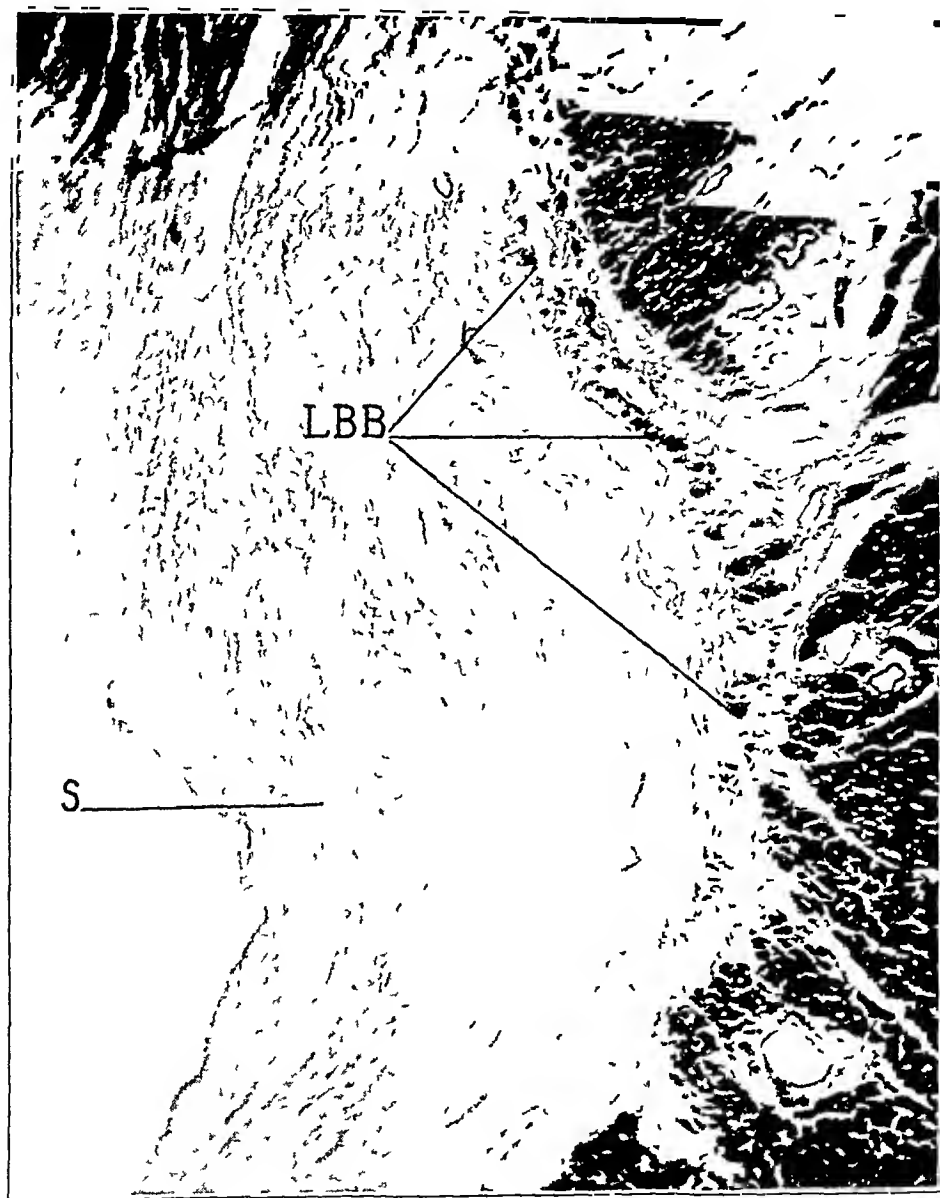


Fig 16 (case 3) —Section 309, block 2, showing in horizontal cross-section the remnants of the left bundle branch (*LBB*) lying beneath the greatly thickened endocardium, $\times 54$

cardium of all the chambers showed patchy whitening, which was most marked on the left side of the interventricular septum. Histologic study showed diffuse and extreme fibrous scarring of the myocardium and thickening and fibrosis of the walls of the intramyocardial arteries, especially of the medial coat. The auriculo-ventricular node was slightly fibrotic, but the bundle of His was fibrotic to the

extent of about 50 per cent of its substance in its distal half. The left bundle branch was represented by a few fibers lying beneath the thickened fibrous endocardium, these almost disappeared in the lower half of the septum. The right bundle branch became progressively more fibrotic and was completely replaced by dense fibrous tissue in its distal half.

Comment—The pathogenesis in this most remarkable case was not clear, but it seems probable that here again it was due to old rheumatic

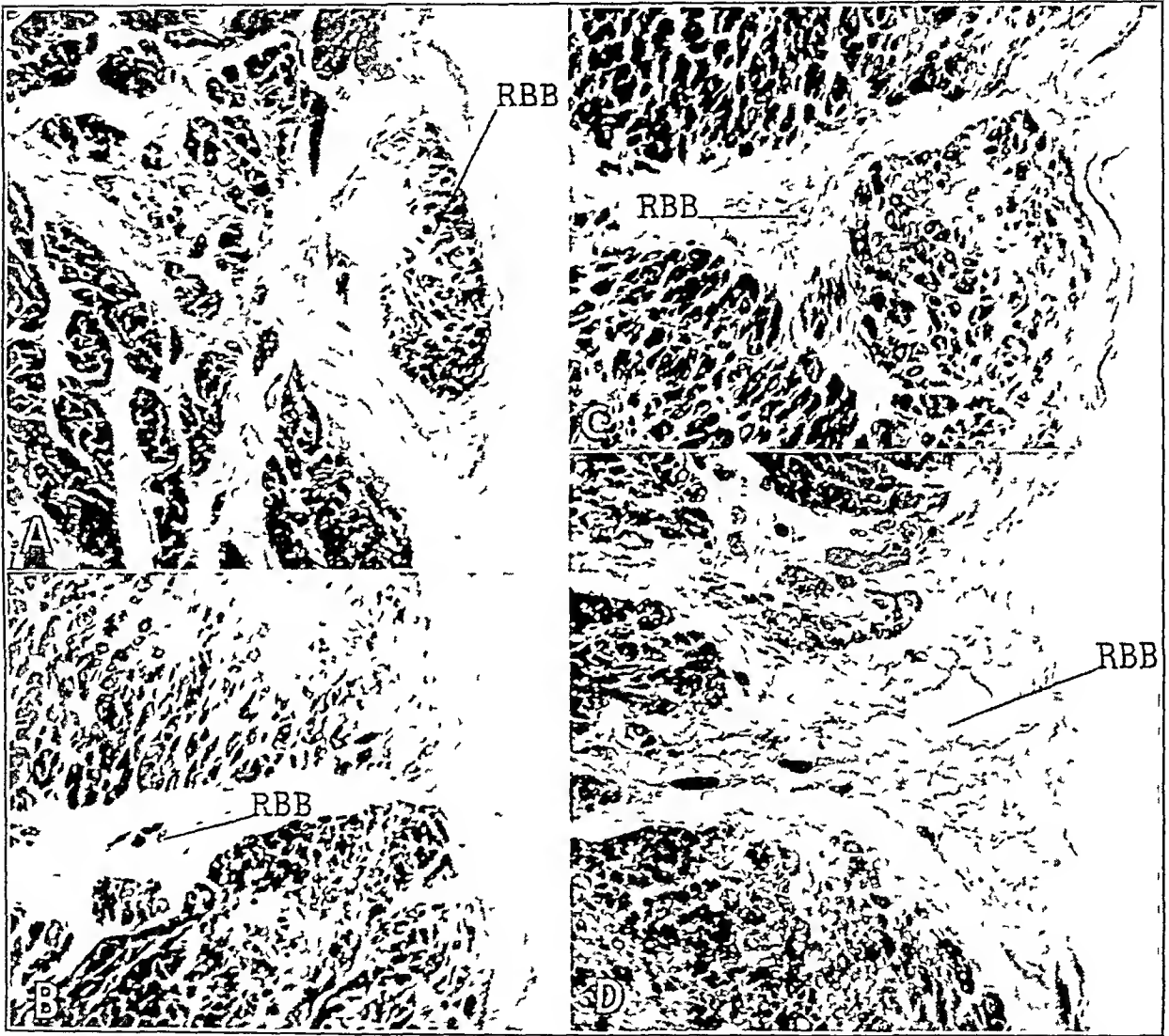


Fig 17 (case 3) —*A*, section 135, block 3, showing in horizontal cross-section moderate fibrosis of the first portion of the right bundle branch (*RBB*). *B*, section 961, block 3, showing only a few fibers remaining in the intramyocardial portion of the right bundle branch, which is adjacent to a small myocardial scar. *C*, section 1,030, block 3, showing complete replacement of the intramyocardial portion of the right bundle branch by fibrous tissue. *D*, section 1,273, block 3, showing the right bundle branch still completely replaced by fibrous tissue in its third, or subendocardial, portion. Compare *D* with figure 20, which shows a relatively normal right branch in about the same region. All sections ($\times 25$) show the fibrotic condition of the myocardium, which, however, is not as marked as at other points.

arteritis and endocarditis. There was definite widespread arterial disease of a kind not due to ordinary arteriosclerosis. The absence of valvulitis, however, threw some doubt on the assumption of a rheumatic etiology. The hypertrophy of the chambers most affected in mitral valvulitis, namely, the left auricle and the right ventricle, was extraordinary, in view of the absence of mitral disease. However, the left ventricle and the interventricular septum were also hypertrophied. The case suggests that disease of the coronary arteries and of the myocardium are capable of producing cardiac hypertrophy.

The extensive destruction of both bundle branches was astounding, but although it was almost unbelievable that the left bundle branch could conduct at all, which it did not do at times, there was no question as to the inability of the right branch to function.

CASE 4 (Army Medical Museum accession no 48678) —*Clinical Record*—The patient was a woman aged 65 years. She had apparently been in good health until a year before admission to the Georgetown University Hospital, on Jan 5, 1936, three days before death. For a year she had had dyspnea on exertion and had received digitalis, the use of which for some reason had been discontinued. In September 1935 dyspnea reappeared, and she was digitalized and ordered to bed by another physician. She improved, but two weeks before her admission to the hospital the dyspnea increased. The day before entry she experienced a sudden "choking pain" over the upper sternal region which radiated around the neck. The pain increased, and when the physician saw her he noted "moderate signs of shock and orthopnea." The temperature was 98.6 F, the pulse rate 100 per minute and the blood pressure 185 systolic and 90 diastolic. The heart did not appear to be enlarged, there was a soft systolic apical murmur. Crepitant rales were heard at the bases of the lungs. An injection of morphine (0.03 Gm) relieved the pain. During the day a pericardial friction rub was noted in the midsternal region, and the patient became cyanotic and more dyspneic. The systolic blood pressure fell only 6 mm of mercury. The patient was admitted at 2:30 a. m., the diagnosis being acute coronary occlusion. She was stuporous, and the findings already noted were verified. The axillary temperature was 99 F, the pulse rate 90 per minute and the respiratory rate 12 per minute. In a few hours the blood pressure had fallen to 142 systolic and 60 diastolic.

An electrocardiogram showed a rate of 90, sinus rhythm, increased amplitude of the main ventricular complex and of the T wave, left axis deviation, a PR interval of 0.24 second, a QRS amplitude of 0.1 to 0.13 second and the T wave in a direction opposite to that of the main ventricular complex in the three conventional leads (fig 18). The interpretation was "first degree auriculoventricular heart block, left axis deviation and intraventricular block of the left bundle branch type."

Urinalysis showed a specific gravity of 0.01, 4 plus albumin and a few leukocytes and erythrocytes. The hemoglobin value was 33 per cent, the erythrocytes numbered 1,960,000 per cubic millimeter of blood, with considerable poikilocytosis and anisocytosis, and the leukocytes numbered 10,000 per cubic millimeter of blood, with 85 per cent polymorphonuclear neutrophils. The nonprotein nitrogen content was 180 mg per hundred cubic centimeters of blood.

An additional diagnosis of severe renal insufficiency was made.

The patient became comatose, and the cyanosis, orthopnea and pulmonary rales increased. The venous pressure was 205 mm of saline solution (Griffith method). The temperature, after rising to 100 F by axilla, dropped to 96.8 F, and the pulse rate, after rising to 100, dropped to 70 per minute. The blood pressure dropped to 110 systolic and 54 diastolic just before death.

Necropsy—Besides the heart, the viscera of interest were the kidneys, which were markedly contracted and granular (one weighing 55 Gm and the other 90

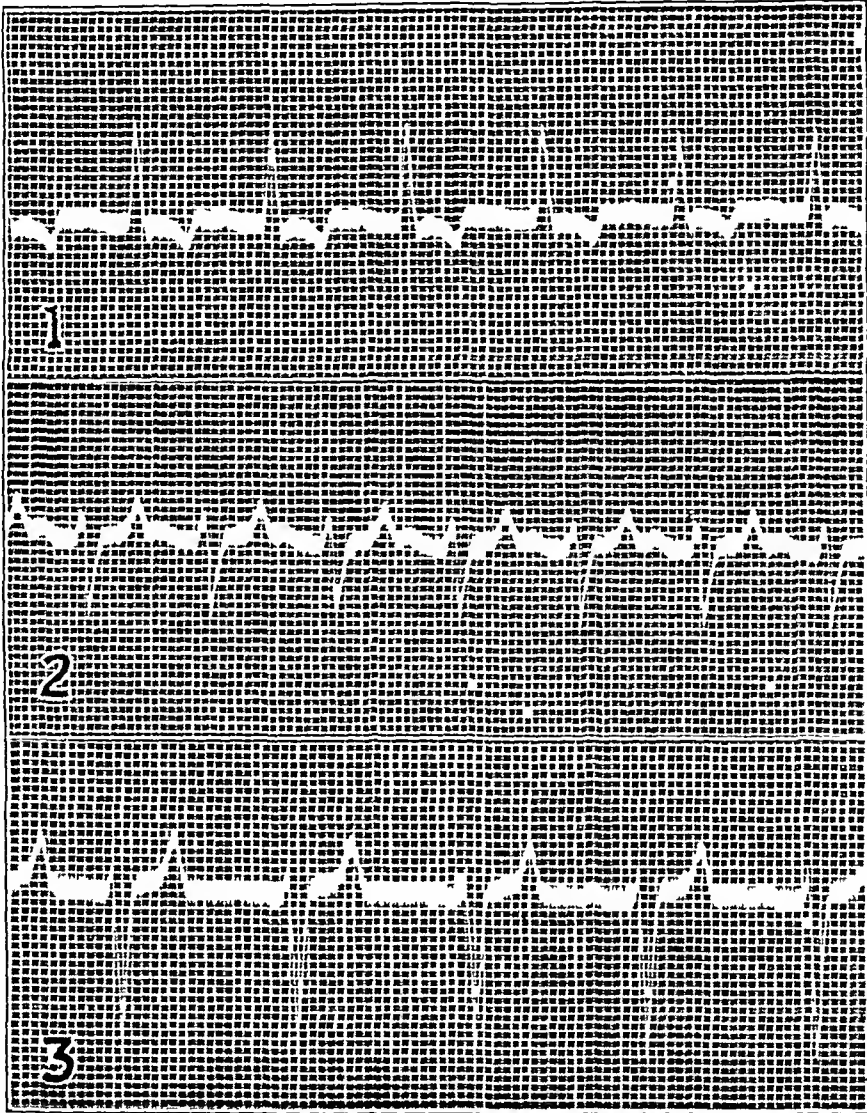


Fig 18 (case 4)—Incomplete left bundle branch block, with QRS intervals of 0.1 to 0.13 second and a PR interval of 0.24 second

Gm) and the lungs, which presented edema of the lower lobes. Microscopically the kidneys were typical secondarily contracted organs.

Gross Examination of the Heart The heart weighed 460 Gm. There was a thin deposit of fibrin on the epicardium. The left ventricle was moderately hypertrophied, its thickness was 1.5 cm in the upper half. The right ventricle was 0.5 cm thick in its upper half, and the interventricular septum was 1.7 cm thick and wider than usual. The myocardium on section appeared normal. The

valves were all apparently normal, and the valvular orifices were of normal circumference. The coronary arteries were all patent and even a little larger in diameter than normal, they showed only moderate atherosclerotic change. The root of the aorta likewise presented only moderate atherosclerotic alteration.

Histopathologic Study of the Heart Blocks were removed from the heart exactly as they were from the heart in case 2 and were prepared, cut, mounted and stained practically in the same manner. Block 1 was cut into 2,510 sections, block 2 into 1,590 sections, block 3 into 1,390 sections and block 4 into 1,530 sections, making a total of 7,020 sections. The auricular myocardium showed little increase in interstitial connective tissue, no more, in fact, than is usually seen in the hearts of most patients of this age. The ventricular myocardium throughout contained a slight excess of interstitial connective tissue also but probably no more than is usually seen in the hearts of most patients of this age. The intramyocardial arteries and arterioles in general appeared likewise to be no more degenerated than usual. Only one vessel was distinctly abnormal, namely, a septal artery running in the ventricular myocardium just beneath the central fibrous body. The wall of this vessel was thickened, and the lumen was reduced in diameter about 50 per cent. This artery gave off a relatively large branch, which passed downward and laterally to the left subendocardial region. One small artery in the auricular myocardium and another in the ventricular were also somewhat abnormal, they suggested superficially the rheumatic arteritis in case 1, with the media disorganized by fibrous tissue and the lumen decreased in diameter. However, it did not appear that there was sufficient vascular disease to be of any great significance.

The auriculoventricular node contained about the same slight degree of excess interstitial connective tissue as the myocardium in general. The greater portion of the auriculoventricular bundle was similar to the node, but as it continued on into the right bundle branch it was about 15 per cent fibrous tissue. The right bundle branch soon became definitely abnormal, in that it was about 40 per cent fibrous tissue, but most of this fibrous tissue was in the right half of the cross-section of the branch, where it had replaced the greater part of the conducting fibers (fig 19). This fibrosis involved only about 3 mm of the branch, after which it rapidly decreased, leaving the branch relatively normal throughout the remainder of its course (fig 20).

The left bundle branch soon after its origin from the bundle of His showed distinct changes throughout its entire length and breadth. This branch was much more extensive than usual and was not distinctly separated into anterior and posterior divisions until it was low down in the septum. Some parts of it were thin, others were thick. The main abnormality consisted of an extensive but varying increase of interstitial connective tissue, which in some places was dense and separated the Purkinje fibers considerably (fig 21), while in other regions in the same and in different planes it was thin and did not separate the muscle fibers much. This fibrosis was observed to be confined to the subendocardial region and did not involve the septal myocardium. The fibrous tissue was thicker on the endocardial side of the branch than on the myocardial side. Throughout its course, however, the fibers of the left bundle branch, even where embedded in the densest fibrous tissue, appeared fairly normal in structure. An interesting feature was the increase in thickness of the smooth muscle layer of the endocardium, which, however, varied considerably in different parts of the endocardium. Another interesting feature was the presence of an offshoot of Purkinje fibers from the left bundle branch at about the junction of the upper and middle thirds of the septum. This offshoot was as thick as the bundle branch and passed down

a short distance into a cleft in the myocardium (fig 22) Although most of the sections of this region were stained, it did not appear that this offshoot went any great distance into the septum This is the first time I have seen such a formation The amount of fibrous tissue in the left bundle branch decreased



Fig 19 (case 4) —Section 70, block 2, showing in horizontal cross-section moderate fibrosis of the right bundle branch in its first portion, $\times 92$

considerably in the lower region, where the elements of the branch passed over to the bases of the papillary muscles

Summary—A woman aged 65 years had had dyspnea for a year A few days before death, severe pain developed in the upper portion of the sternum, and

she rather rapidly passed into coma. The blood pressure, which had been moderately elevated, dropped progressively. There were orthopnea, some cyanosis, rales in the bases of the lungs and a little fever. The nonprotein nitrogen content was 180 mg per hundred cubic centimeters of blood. The electrocardiogram showed prolongation of the PR interval, left axis deviation and the T wave in all three leads in a direction opposite to that of the main ventricular complex. There was not much spread in the QRS complex, and no notching was seen. Necropsy revealed markedly secondarily contracted kidneys. The heart was moderately hypertrophied. The coronary arteries were not much degenerated, and the myocardium was normal for the patient's age. The auriculoventricular node and bundle were relatively normal, but a short portion of the first part of the right bundle



Fig 20 (case 4) —Section 1,320, block 2, showing in horizontal cross-section the right bundle branch practically normal in its third portion, $\times 89$

branch was moderately fibrotic and the left bundle branch showed extensive but variable interstitial fibrosis, although the Purkinje fibers were well preserved.

Comment —This case was studied because of the incomplete picture of bundle branch block. Some cardiologists would consider the electrocardiographic curves as those merely of preponderance of the left ventricle. However, the lesions of the bundle branches, especially of the left branch, would allow one to suggest that there was some reduction in the conduction time through the branches and certainly more



Fig 21 (case 4) —Section 510, block 3, showing a portion of the left bundle branch embedded in dense fibrous tissue, $\times 140$

in the left than in the right. This relativity of involvement of the branches is important, since it must be rare for one branch alone to be diseased. Also, it does not seem to be necessary to assume that one or the other branch must be completely destroyed to produce distortion of the electrocardiographic curves.

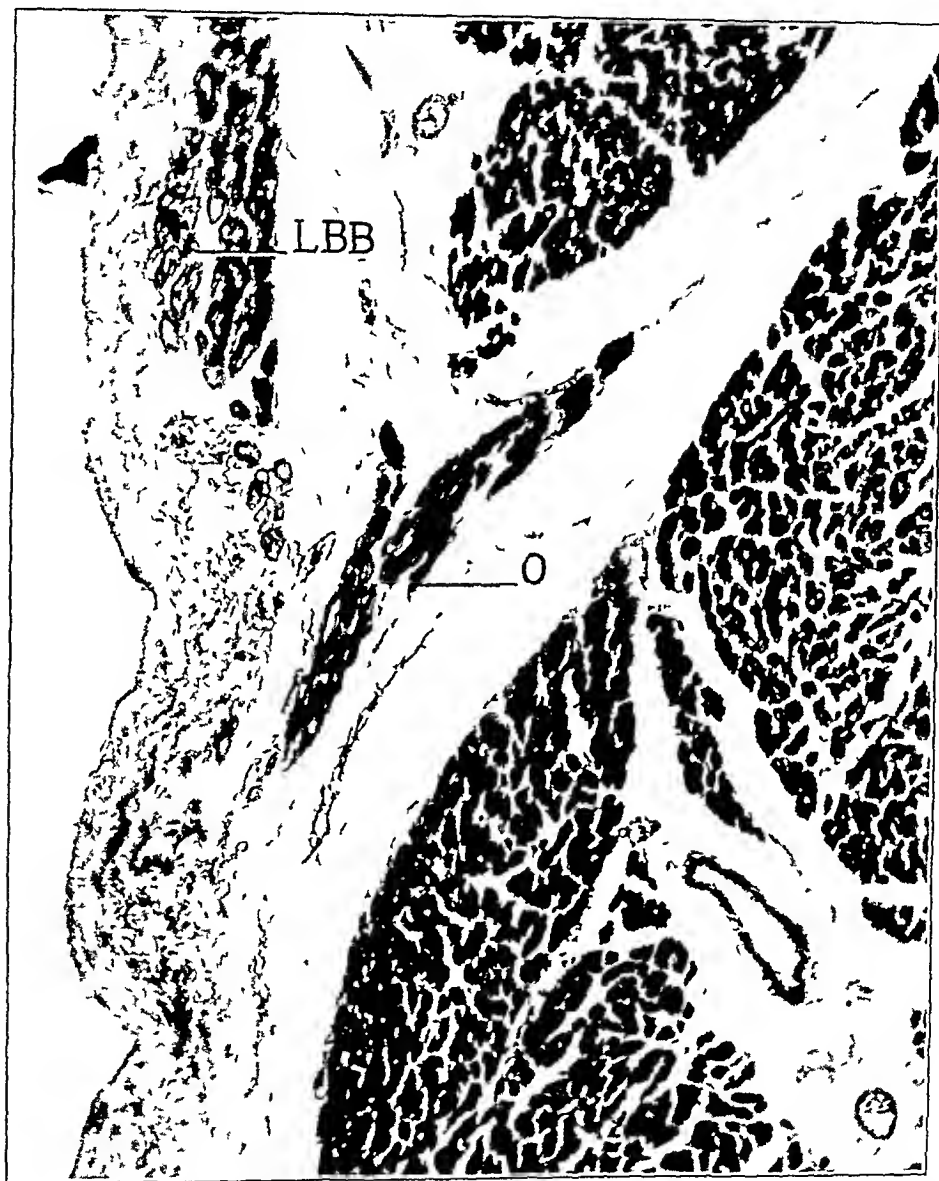


Fig 22 (case 4) —Section 1,240, block 3, showing an offshoot (O) into the myocardium from the left bundle branch, $\times 92$

The pathogenic origin of the lesions of the conduction system in this case is not certain, but the etiologic factor of chronic renal disease with hypertension is clear. Although there was no advanced degree of disease of the coronary arteries, it appears that the involvement of the bundle branches was the result of impaired nutrition.

- It is fair to point out that the electrocardiogram was made shortly before death, a fact which constitutes a weakness in relating the electrocardiographic picture to the lesions in the bundle branches

The abortive offshoot of the left bundle branch observed in this case suggested the presence of communications directly into the myocardium from a bundle branch. This observation is reminiscent of the work of Cardwell and Abramson¹⁵³ (1931), Wahlin¹⁵⁴ (1932) and later Abramson and Margolin¹⁶⁹ (1936) in connection with animal hearts, but it is not conclusive. I have never seen unequivocal communications in the human heart either of the variety found in animal hearts or of the kind described by Mahaim¹⁵¹ in the human heart, although I am willing to believe that minute communications do exist from one side of the septum to the other.

CASE 5¹⁷⁰ (Army Medical Museum accession no 52100) —*Clinical Record*— A Spanish War veteran aged 53 years was found to have heart disease in November 1932, when he entered a hospital for repair of a ventral hernia resulting from appendectomy four years previously. In childhood he had smallpox, diphtheria, scarlet fever and mumps. He was told about four years before admission to the hospital that he had mild hypertension. The hernioplasty was followed by separation of the incision, later abscess formation in the wound and finally a prostatic abscess, which was accompanied with severe systemic symptoms and leukocytosis (25,000 leukocytes). His condition for a time was serious, but he eventually made a good recovery. His blood pressure at that time was 140 systolic and 86 diastolic. He had had attacks of tachycardia. An electrocardiogram made on Jan 18, 1933, showed a heart rate of 144 per minute, a PR interval of 0.16 second, a QRS interval of 0.08 second, an S wave in all leads, the take-off of the ST segment a trifle elevated in leads II and III and a relatively low T wave in all leads.

After leaving the hospital he took a job requiring much exertion. Three months later the ventral hernia recurred. Dyspnea on exertion and attacks of precordial oppression and dull pain developed. However, he did not reenter the hospital until March 5, 1936. Examination showed the blood pressure to be 110 systolic and 68 diastolic, the heart sounds were normal, and the liver was not enlarged. Roentgenographic study revealed evidence of a chronic duodenal ulcer. The prostate gland was enlarged and boggy. He remained in the hospital five weeks, receiving prostatic massage and general treatment. On March 23, he had an attack of ventricular tachycardia (fig 23 A), which ceased after the administration of 5 grains (0.33 Gm) of quinidine sulfate. An electrocardiogram (fig 23 B) then showed left axis deviation, with an inverted T wave in lead I and a QRS interval of 0.12 second. Lead IV showed a low take-off of the ST segment. He was discharged on April 11 in fairly good condition. However, he noted swelling of the feet almost immediately after discharge, when he resumed his work as a night watchman. Attacks of dyspnea, palpitation of the heart and precordial pain became more frequent. By November he could hardly get his shoes on because

169 Abramson, D. I., and Margolin, S. A Purkinje Conduction Network in the Myocardium of the Mammalian Ventricles, *J. Anat.* **70** 250, 1936

170 Major John G. Knauer gave me permission to use the records of this case and to study the heart.

of edema Before the end of that month the edema involved the whole of both lower extremities He began to expectorate blood-tinged sputum and became orthopneic The abdomen became swollen A physician gave him digitalis

On December 5 he reentered the hospital, presenting the picture of advanced congestive failure The blood pressure was 105 systolic and 60 diastolic The heart sounds were weak There was a peculiar impure quality to the first sound, which resembled the dull twang of a bowstring Later a protodiastolic gallop rhythm appeared The electrocardiogram was then different from the preceding one, there was much lower amplitude, and the QRS complex was much broader (0.16 second, fig 23 C) Laboratory studies revealed evidence of mild renal insufficiency The usual treatment was instituted, but all the manifestations of congestive heart failure progressed to an extreme degree, and death occurred on December 11

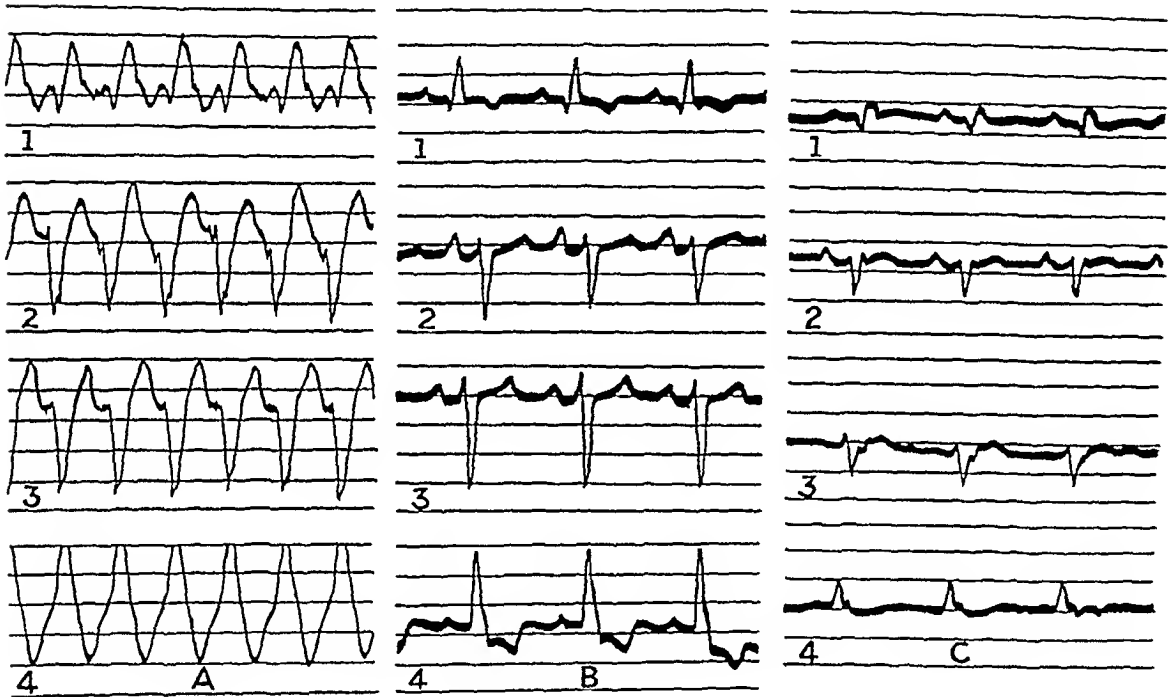


Fig 23 (case 5) —*A*, paroxysmal ventricular tachycardia, *B*, left bundle branch block, with a QRS interval of 0.12 second, shown after the cessation of ventricular tachycardia, nearly nine months before death, *C*, a lower voltage and a QRS interval of 0.16 second a few days before death

The following clinical diagnosis was made by Major Knauer generalized arteriosclerosis, with severe coronary involvement, cardiac hypertrophy, with myocardial degeneration, fibrosis and herniation of the left ventricular wall and severe cardiac decompensation, secondary to coronary arteriosclerosis, moderate chronic suppurative prostatitis, large right ventral hernia, complete bilateral (large on the right and small on the left) direct-indirect inguinal hernia that was reducible, moderate chronic chorioretinitis of the right eye, moderate bilateral pinguecula, chronic ulcer of the duodenum, terminal bronchopneumonia of the lower lobes of the lungs, and moderate nephrosclerosis

Necropsy—Necropsy was performed by Major Don Longfellow approximately eight hours after death occurred There was marked arcus senilis The scleras

were icteric. The mouth was edentulous. There was severe pitting edema of the lower extremities and of the sacral region. The nail beds were slightly cyanotic. The right pleural cavity contained a large amount of thin brownish fluid, and there were delicate adhesions posteriorly. The lower and middle lobes of the right lung were covered with a fibrinous exudate. In the lower portion of the upper lobe there was a large blackish red infarct, and in the pulmonary artery leading to this area there was a thrombus which was firmly attached to the intima and which completely occluded the vessel. The lower portion of the lower lobe of the left lung was dark red, airless and apparently consolidated. The heart was moderately enlarged and was displaced to the left by the pleural effusion in the right hemithorax. The abdomen contained a large amount of thin clear straw-colored fluid. The liver weighed 1,700 Gm, and its cut surface presented a distinct "nut-meg" pattern. The kidneys were about normal in size and had a finely granular surface, with some superficial puckered scars. The cut sections showed cortical cysts, indistinct differentiation of cortices and pyramids and indistinct cortical striations. The prostate was much enlarged, and in the left lobe there was a honeycombed area, other portions of the cut surfaces were yellowish pink and homogeneous. The seminal vesicles were distended with thick granular material and were unusually thick walled. The first portion of the duodenum contained a small depressed ulcer, 4 mm in diameter. There was moderately severe generalized arteriosclerosis.

Gross Examination of the Heart The heart weighed 550 Gm. The lower anterior surface of the epicardium was roughened where adhesions to the pericardium had been separated. There was a normal amount of epicardial fat. All the chambers were dilated. The anterior descending branch of the left coronary artery was completely occluded below its first 2 cm by an old yellowish thrombus for about 2 cm, beyond which it was occluded by a soft purplish clot. The wall was thickened and calcified. The lumen of the portion proximal to the thrombus was dilated. The first 3 cm of the circumflex branch of the left coronary artery was greatly dilated and sclerotic and was filled with a fresh thrombus, beyond this its lumen was small, and the wall was asymmetrically thickened. The right coronary artery was only moderately sclerotic and was patent throughout. The left ventricle was dilated, grade 3, with a rounded apex, and its papillary muscles were moderately hypertrophied. The lower half of the interventricular septum showed a deep depression filled with an old mural thrombus (fig 24). The upper edge of this depression ran obliquely downward from front to back toward the apex. The lower portion of the anterior wall and the rounded apical portion of the ventricle were thin and fibrous, being 2 mm thick and containing practically no muscle. The thickness of the wall near the base of the ventricle was 1.8 cm. On cut section the myocardium here did not appear to be fibrotic. The endocardium of the left side of the interventricular septum between the aortic valve and the mural thrombus was smooth and glazed. The mitral valve was apparently normal except for moderate atheromatosis of the aortic cusp. The mitral orifice was 12 cm in circumference. The aortic valve appeared to be normal, and the aortic orifice measured 7 cm in circumference. The root of the aorta was moderately atherosclerotic. In the arch of the aorta there were numerous large calcified plaques, a condition which was maintained throughout the thoracic and abdominal portions. The right ventricle was dilated, grade 3. Its wall was 0.6 cm thick in the upper half. In the apical region of its cavity a mural thrombus was loosely attached to the wall, its shape was that of a long curled cylinder, suggesting its origin in a vein. This appeared to be the source of the embolus in the right lung. The endocardium of this ventricle appeared normal. The

tricuspid valve was apparently normal, and the right venous ostium measured 13.6 cm in circumference. The pulmonary valve also appeared to be normal, and its orifice measured 8.5 cm in circumference.

Histopathologic Examination of the Heart Five blocks of tissue were removed from the auriculoventricular and from the interventricular septum, the upper 3 of which included practically all the microscopically recognizable portion of the conduction system. These blocks contained the entire thickness of the septums. The upper 3 blocks were embedded in paraffin, and horizontal sections, 10 microns thick, were cut serially from above down. All the sections were mounted, and every tenth section was stained with Masson's trichrome preparation. There were 1,520 sections made from block 1, 1,720 from block 2 and 1,000 from block 3, making a total of 4,240 sections.

The auriculoventricular node and bundle and about 1 cm. of the bundle branches were included in the sections of block 1. The upper portion of the auriculo-



Fig. 24 (case 5)—The opened left ventricle, showing the scarred portion. A mural thrombus is seen in the depressed portion of the interventricular septum. The apical region bulges, almost aneurysmally.

ventricular node was composed of interlacing fibers that were much disrupted and that were separated by fibrous tissue and surrounded peripherally by fatty connective tissue containing little auricular myocardium. The lower portion of the node was more compact but contained somewhat more than the normal amount of fibrous and fatty connective tissue. The auriculoventricular bundle was also moderately infiltrated with fibrous connective tissue and was partly replaced by fatty connective tissue. Its capillaries were engorged with blood. The artery to the node and bundle was considerably degenerated, its wall being thickened and fibrous and its lumen narrowed by intimal fibrous tissue. The myocardium adjacent to the bundle was fibrotic. The auricular myocardium was fibrotic in the posterior half of the septum, and its largest artery had a thick, dense, fibrous wall and a small irregular lumen. The root of the tricuspid valve contained

numerous capillaries, plasma cells and fibroblasts. The first portion of both right and left bundle branch appeared moth-eaten because of fibrosis and fat invasion. The very first portion of the left bundle branch was extremely thin and almost not recognizable, but it rapidly became larger, although it remained fibrotic. The endocardium on the left side of the interventricular septum soon became thick and fibrous. The fibers of the left bundle branch were embedded in this fibrous tissue, and many of them appeared to have become necrotic and disintegrated because of compression, others appeared relatively normal. In some places there were relatively few Purkinje fibers remaining. The right bundle branch rapidly left its subendocardial position and became deeply intramyocardial. In most of block 1 about 15 per cent of the fibers were replaced by fibrous connective tissue. There was moderate patchy fibrosis of the interventricular septum. Only small vessels were seen in most of block 1. They were often surrounded by an abnormally thick zone of fibrous tissue, and the walls of some were moderately or even severely fibrotic, whereas others had fairly normal walls.

In the upper part of block 2 the left bundle branch became even more degenerated, the posterior half showing only a small number of fibers which appeared capable of functioning at all (fig 25). The right bundle branch also became rapidly more fibrotic, until about 50 per cent of its fibers had been replaced by dense interstitial fibrous connective tissue (fig 26). At no point, however, did the right branch appear to be as severely compromised as the left. The right branch, in fact, rapidly became less fibrous again, and as it approached the endocardium it became almost normal, remaining so as far as it could be followed subendocardially. The left branch, on the other hand, continued to be greatly degenerated by the invasion of fibrous tissue, although there was considerable variation in the degree of involvement. The surrounding connective tissue always remained dense, however. In block 2 the dense myocardial scar of an old infarct began to appear and grew larger with succeeding sections. The scar was patchy and most dense in the left side of the septum in its anterior half. The patches of scar tissue contained small thin-walled blood sinuses. The small arteries in the myocardium often had thick fibrous walls and small lumens. In the lower half of block 2 most of the anterior half of the left bundle branch had disappeared in the scar of the infarct. The posterior half of the branch had become larger and more cellular but was still embedded in dense fibrous tissue.

In block 3 the right bundle branch could not be found, and since in its upper part the right side of the septum was fairly normal, especially the endocardium, it was assumed that it had spread out normally beneath the endocardium and could not be recognized, as is frequently the case. The old scar in the septum grew larger, as did also the mural thrombus. The left bundle branch was present only in the posterior half and lower only in the posterior fourth of the septum. The branch was thicker, however, and contained more fibers on cross-section. As section 1,000 was approached the scar extended almost across the septum anteroposteriorly and involved most of the thickness of the septum, but more on the left than on the right half. The scar was not entirely solid but contained islands of myocardium. Only a small group of Purkinje fibers of the left branch finally remained at the very posterior part of the septum, and these were still embedded in fibrous tissue.

Summary—A man aged 53 years was known to have had heart disease for four years and died of congestive heart failure. An electrocardiogram made ten months before death showed ventricular tachycardia, after cessation of the tachycardia an electrocardiogram showed left axis deviation, with an inverted T wave

in lead I and a QRS interval of 0.12 second. Another, made shortly before death, showed low voltage and a QRS interval of 0.16 second. The heart weighed 550 Gm, and all chambers were dilated. There was advanced coronary arteriosclerosis, with an old thrombus in the anterior interventricular artery and a fresh one in the left circumflex artery. An old infarct in the apical region of the left

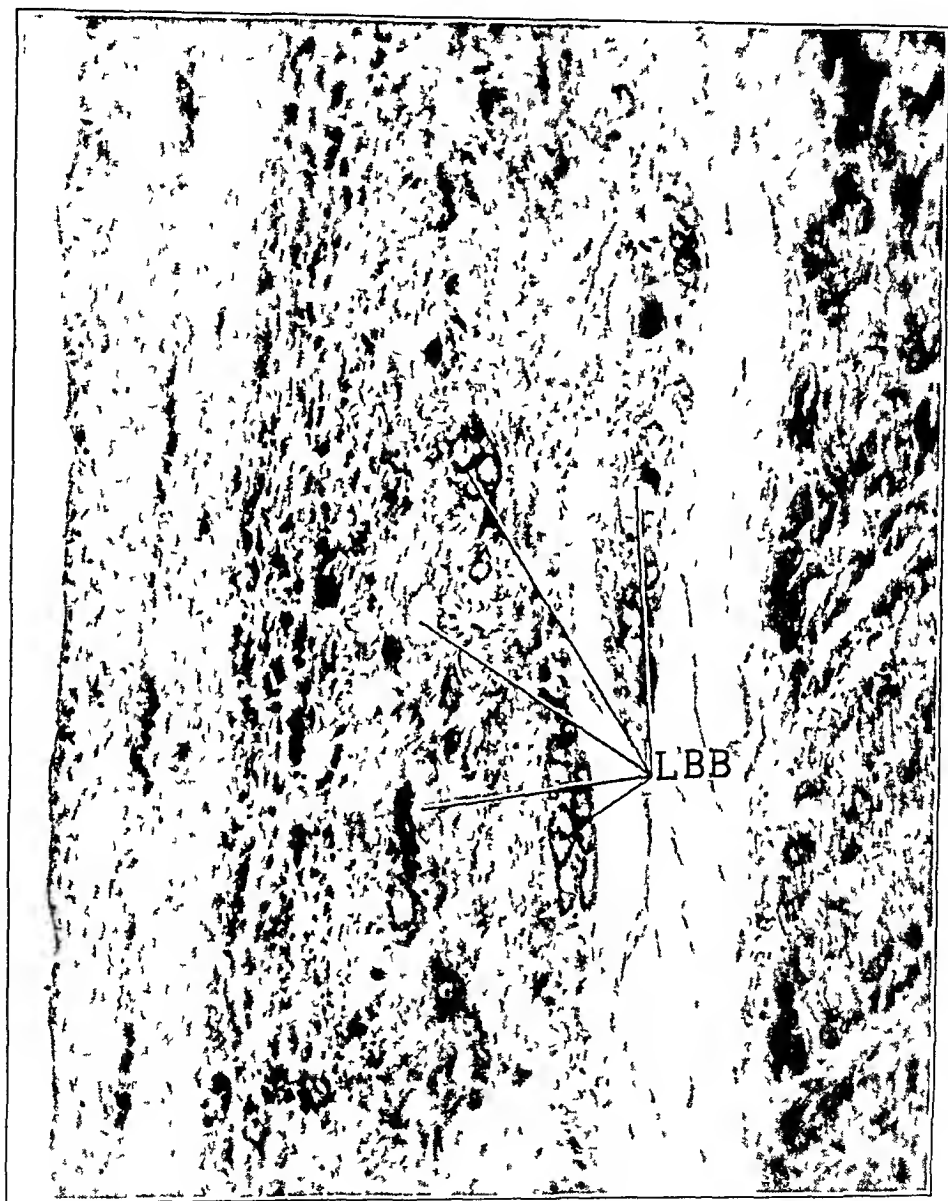


Fig 25 (case 5) —Section 360, block 2, showing in horizontal cross-section a portion of the left bundle branch embedded in and almost completely replaced by fibrous tissue, $\times 137$

ventricle and in the lower anterior portion of the interventricular septum had caused marked thinning of these portions. A study of 4,240 serial sections of the conduction system showed that the auriculoventricular node and bundle were moderately fibrotic and partly replaced by fatty connective tissue. The right

bundle branch showed moderate fibrosis down to the middle of its intramyocardial portion, in which for a short distance fibrous tissue replaced about 50 per cent of its fibers. Beyond this point it was fairly normal. The left bundle branch was seriously degenerated by dense fibrous tissue in the subendocardial layer, especially in its upper half. In its lower half the anterior division had completely disappeared in the scar of the old infarct, whereas the posterior division, although still compromised by fibrosis, was not as much diseased as it was in its upper half.

Comment—The electrocardiographic pattern in this case, i e, the one made several months before death and after an attack of ventric-

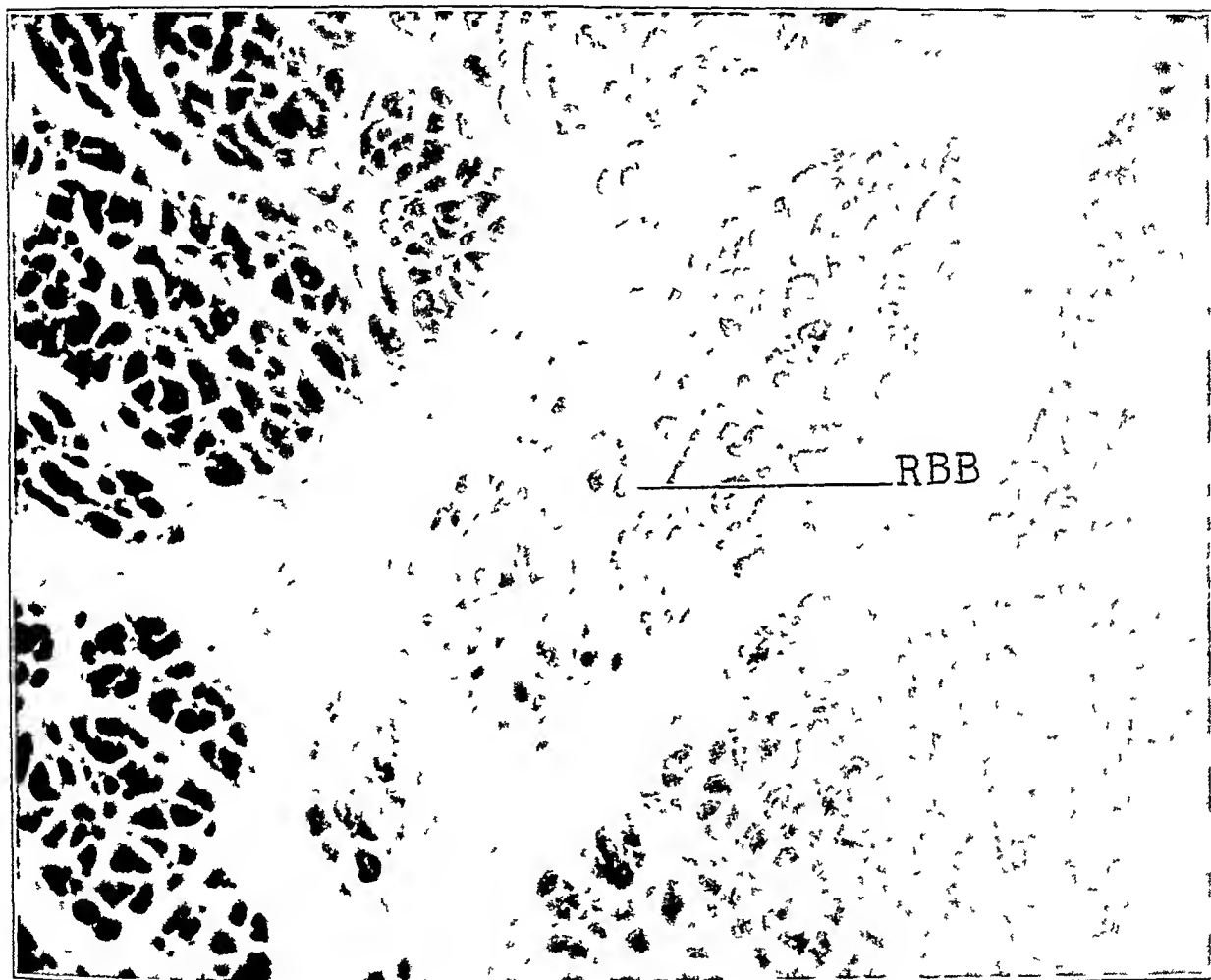


Fig 26 (case 5)—Section 160, block 2, showing in horizontal cross-section the right bundle branch replaced in its upper portion by about 50 per cent by dense fibrous tissue, $\times 133$

ular tachycardia, represented merely an advanced stage of that in the preceding case. Although both bundle branches were diseased, there was no question as to the one more seriously affected. The left branch, while not completely destroyed at any one level, was so extensively degenerated throughout that, compared with the right branch, the impulses passing through it must have been greatly retarded. Conse-

quently, one is justified in assuming that the degeneration of the left branch played an important role in determining the electrocardiographic pattern

The pathogenic factor in this case is clearcut, being advanced disease of the coronary arteries and old myocardial infarction. The electrocardiographic curves seen in this case are so frequently observed in cases in which the gross morbid anatomic picture is very similar that one may be pardoned for concluding that in most of these cases there is considerable degeneration of the left bundle branch.

CASE 6¹⁷¹ (Army Medical Museum accession no 52410) —*Clinical Record* — The patient, a Negro aged 40 years, was admitted to the Hines Hospital, Hines, Ill., on March 11, 1936, for treatment of heart disease. He had had the usual diseases of childhood, pneumonia, "rheumatism" and gonorrhea. He became dyspneic in February 1935 and later had edema of the feet and a cough. He worked until July 1935 and after two weeks' vacation worked again for six weeks, after which he was unable to work. On admission to the hospital he was found to be moderately dyspneic and to have slight edema of the feet. The apex impulse was heaving and the heart moderately enlarged. Gallop rhythm was present at the apex. The cervical veins were distended, there was evidence of passive congestion of the lungs and the liver was palpable. The peripheral arteries were severely sclerosed. The heart rate was 110 per minute, and the blood pressure was 150 systolic and 125 diastolic.

An electrocardiogram, made on March 13, showed regular sinus rhythm, a rate of 120 per minute, a PR interval of 0.16 second, a QRS complex of moderate amplitude in leads I and III, of low voltage in lead II and of 0.14 second duration, grossly notched and with the main component upright in lead I and down in leads II and III, and a T wave that was intimately joined to the main complex, especially in leads I and III, and directed oppositely to them (fig 27 A).

He received the usual treatment for congestive failure and was somewhat improved thereby. A second electrocardiogram, made on June 10, was similar to the first except that the QRS complex was upright in lead II. All the usual laboratory tests gave normal results. A roentgenogram showed moderate hypertrophy of the left ventricle.

From June 11, when he left the hospital, until Jan 22, 1937, when he was readmitted, he remained in about the same condition. On his second admission to the hospital he was found to have more dependent edema and ascites. There was greater dyspnea. The apex impulse was felt in the left anterior axillary line. Gallop rhythm was present at the apex, and the heart rate was 100 per minute. The blood pressure at first was 110 systolic and 90 diastolic, later it was 90 systolic and 80 diastolic. A roentgenogram showed marked enlargement of the cardiac shadow, the aortic shadow measuring 7 cm, the greatest cardiac diameter 19 cm and the transverse thoracic diameter 26 cm. There were large bullae on the dorsum of the feet, which were cold, and the skin of the legs was abnormally dark. Pulsations were not palpable in the left femoral artery, and none was palpable in the vessels of either foot. There were moderate anemia and moderate leukocytosis. The urine contained a heavy trace of albumin, the

¹⁷¹ Drs Philip P Matz and Edward W Hollingsworth, of the Veterans' Administration, gave me permission to study the heart in this case and to make a report.

nonprotein nitrogen content of the blood was 120 mg per hundred cubic centimeters. The electrocardiogram made on January 25 was essentially the same as the first one, made over ten months before.

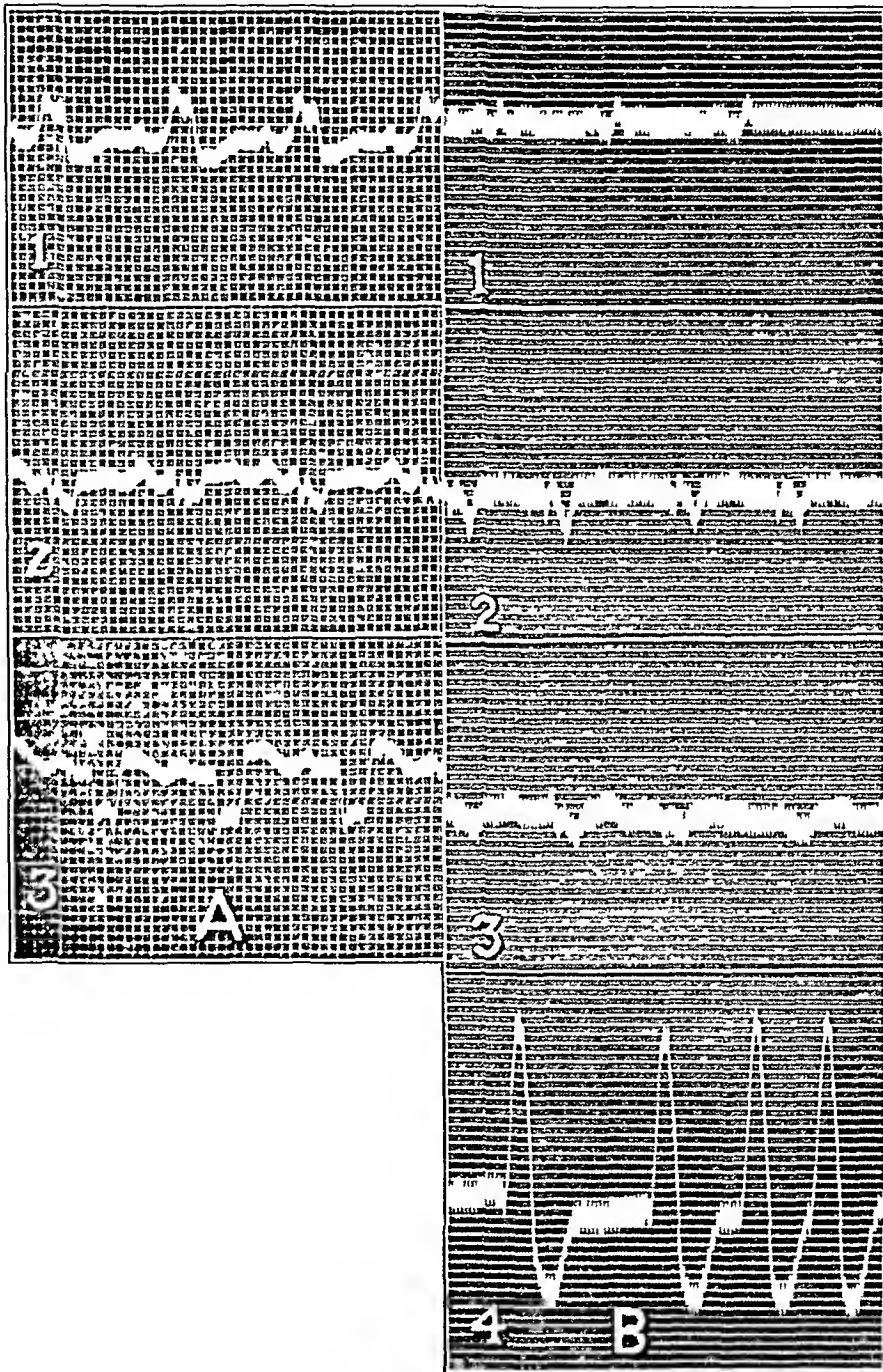


Fig 27 (case 6) —*A*, left bundle branch block, with a QRS interval of 0.14 second, eleven months before death, *B*, auricular fibrillation, with low voltage except in lead IV and a QRS interval of 0.16 second, four days ante mortem.

The diagnosis of hypertensive heart disease and probable occlusion of the coronary arteries was made. It was also thought that there was thrombotic occlusion of both femoral arteries, with early gangrene of the feet. The course was rapidly downhill. The electrocardiogram made on February 5 was different.

from the previous ones (fig 27 B) It showed auricular fibrillation, low voltage except in lead IV, a grossly notched QRS wave of 0.16 second duration in leads I to III, a large QRS complex in lead IV and a T wave upright in leads I to III and inverted in lead IV Death occurred on February 9

Necropsy.—In addition to the cardiac abnormalities the following conditions were noted extensive adhesions of the pleurae, abscesses in the lower portion of the upper lobe of each lung, containing grayish, foul-smelling material, ascites (about 1,000 cc of clear fluid), whitish yellow plaques in the aorta, and adherent thrombi in both iliac arteries, the one in the right artery extending up to the

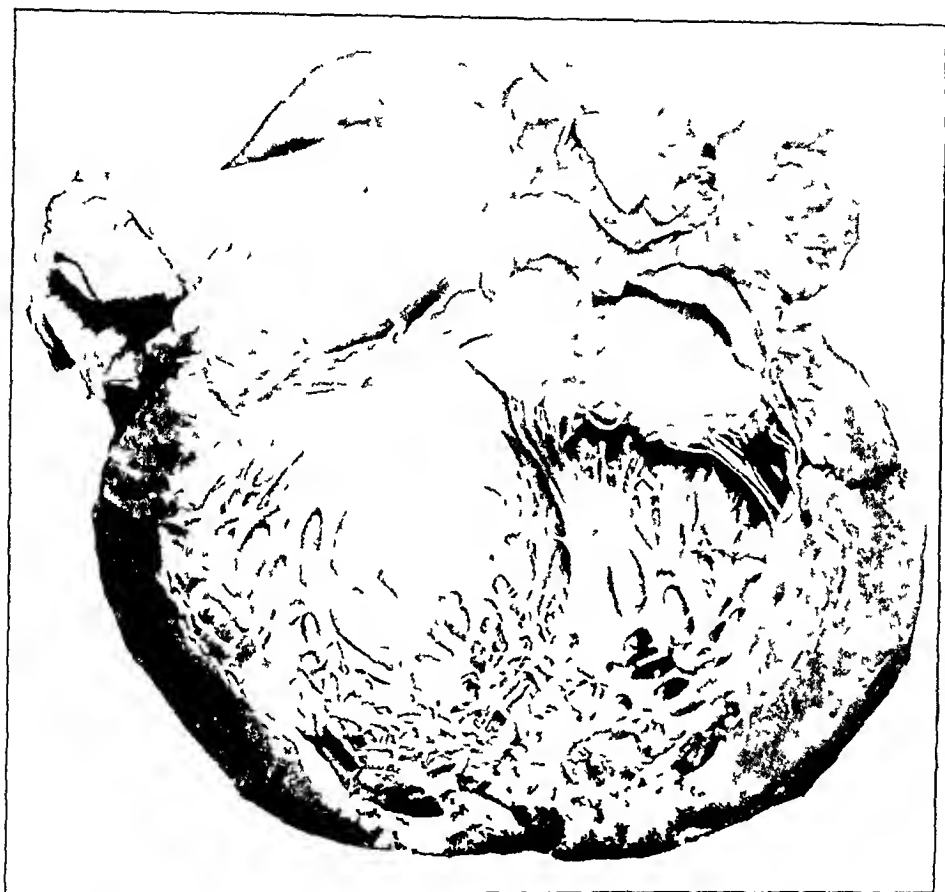


Fig 28 (case 6) —The opened left ventricle, showing hypertrophy and extreme dilatation, with a small mural thrombus in the apical region

bifurcation of the aorta and the one in the left extending below Poupart's ligament The spleen weighed 210 Gm, the liver 1,560 Gm and the kidneys 165 and 195 Gm, respectively

Gross Examination of the Heart The heart weighed 575 Gm The pericardium was normal, with little fat All four chambers were greatly dilated, the left ventricle tremendously so (fig 28) In the greatly rounded apical portion of the left ventricle there was a mural thrombus, measuring 2 by 2 cm, with a slightly raised and roughened surface It was firmly attached to the posterior wall The endocardium over most of the left surface of the interventricular septum appeared normal, but it was thickened and presented a ground-glass appearance on the anterior wall of the ventricle, over the septum in the apical

region and in the vicinity of the thrombus. The wall of the ventricle near the base was 1.3 cm thick, and on cut section the muscle did not appear abnormal. The aortic and mitral valves were apparently normal. The aortic ring measured 7 cm in circumference and the mitral 9 cm. The root of the aorta was smooth walled. The left auricle contained a mural thrombus on its upper posterior wall, measuring 1 by 3 cm, and a smaller one was present in the auricular appendage. The wall of the right ventricle was 0.6 cm thick near its base. Its endocardium appeared normal. The pulmonary and tricuspid valves were apparently normal, the ring of the former measuring 7 cm in circumference and that of the latter 13.5 cm. The right auricular appendage was large, being 7.5 cm long and 4.5 cm wide. It was filled with thrombi, probably of antemortem origin. In connection with the eustachian valve there was a fibrous thread stretching vertically across the auricle for a distance of 4 cm. A small white thrombus was firmly attached to it at about its middle. The coronary arteries were a little thickened but were not calcified, their lumens were well open, except for agonal thrombi in both anterior and posterior interventricular arteries. The myocardium in general did not appear abnormal, and there was no gross evidence of old or recent infarction.

Histopathologic Examination of the Heart The entire interventricular septum, including the lower portion of the auriculoventricular septum, was excised and divided by horizontal cuts into four blocks. The upper 3 blocks were embedded in paraffin and cut horizontally into sections of 10 microns thickness serially from above down. Block 4, which included the most trabeculated portion of the septum near the apex, was not cut because it would have been almost impossible to recognize the Purkinje fibers in it. From block 1, 970 sections were made, from block 2, 1,530, and from block 3, 1,400, making a total of 3,900 sections. All were mounted, and every tenth one was stained with Masson's trichrome preparation.

The auricular myocardium was moderately fibrotic in patches, and the arteries therein were degenerated, with much intimal thickening and diminution in the size of the lumen. The auriculoventricular node was moderately fibrotic, as was also the auriculoventricular bundle. The very first portion of the left bundle branch was thin and contained only a few separated fibers. Too much importance should not be placed on such an observation, however, since this appearance does not necessarily indicate a pathologic condition. The beginning of the right bundle branch was moderately fibrotic, but like the node and main bundle it contained many normal-appearing conduction fibers. The right branch, however, soon became practically normal in appearance and continued so down to the portion which spreads out subendocardially. The left bundle branch was not completely interrupted at any level. However, it was definitely pathologic in much of its course. The fibers in many places were thin, vacuolated and embedded in dense fibrous tissue of the endocardium (fig 29). The latter, however, was not much thickened. The best looking portion of the branch was the central part, which was thicker than the anterior portion, but its fibers also appeared much more vacuolated than normal. A large portion of this part of the branch entered a sheetlike layer of myocardium, which became separated from the main mass of the septum and gradually worked posteriorly, where it became the posterior division of the branch. As both anterior and posterior divisions broke up, their components entered trabeculae in which the Purkinje fibers formed fasciculi, many of which were embedded in dense fibrous tissue.

The myocardium of the septum had a few small scars scattered through it, but the great bulk of muscle was in good condition. The arteries in the septum were not as much degenerated as they were in the auricle near the central fibrous body.

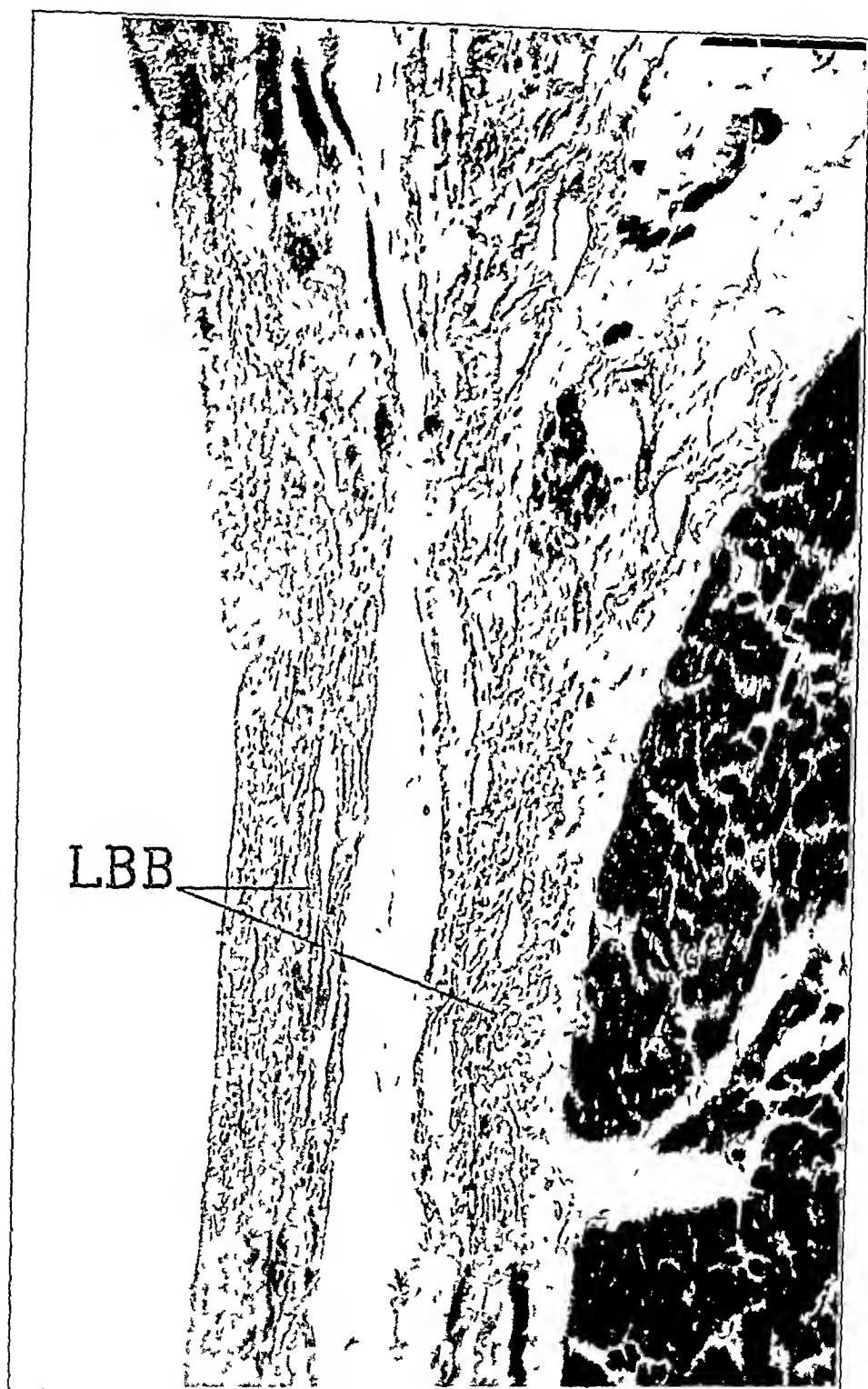


Fig 29 (case 6) —Section 530, block 2, showing in horizontal cross-section a portion of the left bundle branch, with thin fibers largely embedded in dense fibrous tissue, $\times 140$

Summary—A Negro aged 40 years had dyspnea for two years before he died. Edema appeared about six months after the onset of dyspnea. The blood pressure at first was moderately elevated but subsequently was normal. The heart was considerably enlarged. Manifestations of congestive heart failure gradually increased, and terminally there was evidence of renal insufficiency, with occlusion of the femoral arteries and gangrene of the feet. Three electrocardiograms made at intervals during the two years before death showed evidence of left bundle branch block. The electrocardiogram made two weeks before death showed auricular fibrillation and low voltage. The heart was found to be hypertrophied and dilated, especially the left ventricle, which contained a mural thrombus in its apex. The coronary arteries were only moderately sclerosed and contained only agonal thrombi. Histopathologic study revealed small scars in the myocardium. The arteries were not very sclerotic except in the auricles near the central fibrous body. The auriculoventricular node and bundle were moderately fibrotic. The right bundle branch except at its origin, where it was moderately fibrotic, appeared practically normal. The left bundle branch was moderately degenerated but apparently not greatly compromised, much of it was embedded in fibrous tissue, and its fibers were more than normally vacuolated.

Comment—I was greatly surprised in this case to find comparatively little damage to the left bundle branch. It was, however, much more degenerated than the right branch, which was only slightly altered. Had there been a larger scar in the septum one might have concluded that the original electrocardiographic curves were the temporary result of coronary occlusion, with infarction of the myocardium. One would certainly expect more severe degeneration of the left branch in this case than in the 2 preceding cases from a comparison of the electrocardiograms. If one assumes, to begin with, that the electrocardiogram indicates impairment of function of the bundle branch in this case, it is plausible to assume further that there may be greater impairment of function of a branch than is evident histologically.

GENERAL COMMENTS ON CASES STUDIED HISTOPATHOLOGICALLY

Certain points in connection with the 6 cases studied histopathologically stand out clearly. In all there was definite organic disease of the bundle branches, although it was least marked in case 6, in which one would have expected more involvement than was observed. Both branches were affected in each case, but it was possible always to state which of the two branches was more seriously affected. The lesion consisted of fibrosis in all cases. In 4 cases (2, 3, 4 and 6) the lesions of the branches appeared to be independent of adjacent lesions in the myocardium, although there were also myocardial lesions of importance in 2 of these (cases 2 and 3), undoubtedly of similar pathogenic origin. In cases 1 and 5 the main involvement of the branches was clearly due to their position in regions of myocardial disease. In most of the cases it seemed proper to attribute the pathologic condition of the bundle branch and myocardial disease to disease of the coronary arteries. At

this point it may be well to state that many hearts not showing disease of the bundle branches have been studied histologically as controls, so that the observations in most if not all these 6 cases are probably of significance in the production of certain at least of the electrocardiographic abnormalities

Cases 1 to 3 are of great significance in that the electrocardiographic curves said by the American school to typify right bundle branch block were associated with complete destruction of part of the right bundle branch, although there was also severe involvement of the left branch. In cases 1 and 2 the lesions were definitely of rheumatic origin, and in case 3 such an etiologic factor also seemed probable. I believe the lesions affecting the bundle branches and the myocardium in all 3 cases were due to rheumatic arteritis, certainly in cases 2 and 3. The valvulitis in cases 1 and 2 probably had nothing to do with the disease of the bundle branches and in case 3 there was no evidence of valvulitis.

In cases 4 to 6 it appears that the lesions in the left bundle branch were the more important in the production of certain at least of the electrocardiographic abnormalities. These abnormalities would be designated by the American school as evidence of disturbance of intraventricular conduction of the left bundle branch type. The 3 cases are examples of so-called degenerative cardiovascular renal disease. In cases 4 and 6 the degree of disease of the coronary arteries was not great, but in case 5 it was extreme, and the lesions in the bundle branches were due definitely to this. In all 3 cases the brunt of the cardiac strain was borne by the left ventricle. In case 4 the slight increase in intraventricular conduction time appeared to be due to extensive fibrosis compromising but not destroying the left bundle branch. This is therefore a case of incomplete left bundle branch block. In case 5 there appeared to be much greater destruction of the left branch, but one could not state with certainty that the branch was completely incapable of functioning. In case 6, in which a complete lesion was anticipated, the lesions observed did not appear sufficient to cause complete interruption of the passage of impulses through the branch. One might conclude with caution, therefore, that cases of complete cross-sectional destruction of the left bundle branch may be rare but that partial lesions compromising the function of the branch may be common and may produce electrocardiographic alterations typical of left bundle branch block.

In only 1 of these 6 cases (case 5) was it possible to state that there was complete destruction of the anterior division of the left bundle branch, as has been said by Mahaim²⁶ to be so common. Even in this case there was also great involvement of the posterior division. This was the only case in which there was severe sclerosis, with occlu-

sion of the large coronary arteries, of these the anterior descending branch was the most affected. In this case there was also considerable fibrosis of a portion of the right bundle branch, a point well explained by the vascular supply of the branches.

One might attempt to explain why the right bundle branch was the more seriously damaged in the cases of rheumatic disease and the left bundle branch in the cases of cardiovascular renal disease. Perhaps the arteritis of rheumatic etiology, involving more prominently the intramyocardial arteries than the large subepicardial ones, more often affects the entire thickness of the interventricular septum and would be more likely to destroy completely the right bundle branch in its intramyocardial portion than it would the subendocardial portion, i.e., the main portion of the extensive left branch. In cases of cardiovascular renal disease, which includes disease of the coronary arteries or arterial hypertension or both, the brunt of the strain, either vascular or hypertensive, is borne by the left ventricle, therefore, it is fair to assume that the nutrition of the left bundle branch would be much more likely to suffer severely than that of the right branch.

From a study of these 6 cases it appears that the amplitude of the ventricular complex is not entirely dependent on the state of the bundle branches in clinical cases.

COORDINATION OF DATA ON BUNDLE BRANCH BLOCK

A careful weighing of the experimental data on bundle branch block shows more points in favor of the newer terminology for electrocardiographic curves. The difference between the newer American and the older European concept, which involves mainly a reversal of terminology, is explicable on the basis largely of anatomic differences between man and the dog.

A review of the literature on bundle branch block reveals much confusion as to which electrocardiographic curves can properly be designated as typifying bundle branch block and as to which bundle branch is affected. Although the classic curves in cases of bundle branch block are accepted by all, there are many atypical curves of unexplained origin. The pathologist has not kept pace with the electrocardiologist even in connection with the classic curves.

A consideration of the large number of published reviews of series of clinical cases of bundle branch block leads to the following conclusions. Bundle branch block is not uncommon. It occurs much more commonly in persons of middle age and early old age. It is much more common in men than in women. It is often but by no means always associated with definite clinical or physical evidence of heart disease. Left bundle branch block is much more common than right bundle

branch block, but the latter is not as uncommon as was originally thought. Cases of transient, intermittent or "functional" bundle branch block are not uncommon. They usually indicate organic heart disease and would probably be more frequently observed if electrocardiograms were made more frequently in individual cases. A progressive change from normal curves to those indicating bundle branch block might also be observed more often if this were done. A sudden onset of permanent bundle branch block is rarely noted. The association of various degrees of auriculoventricular block with bundle branch block is not uncommon, and auricular fibrillation may also occur in association with it. Premature contractions are, of course, fairly common accompaniments. The prognosis is grave, but many patients have lived for several years after discovery of the condition.

The question as to where curves indicating ventricular preponderance end and those indicating intraventricular block begin is not settled, but it is probable that any increase in the QRS interval over 0.1 second is an indication of disease of one or both bundle branches. Ventricular strain may be important in many cases in determining the direction of the main ventricular complex and the T wave, particularly in leads I and III. The effect of the position of the heart on the form of the electrocardiographic curves should rarely be sufficient to cause much confusion in the interpretation of the curves.

The pathogenic factor in cases of bundle branch block is almost always disease of the coronary arteries, rheumatic or degenerative, or hypertension, as indicated by a review of the literature and the 16 cases reported in this article.

The histogenic factor in bundle branch block is mainly fibrosis due to disease of the coronary arteries or to subendocardial thickening due partly to stretching and strain from hypertension, but the studies performed have been confusing, largely in regard to which bundle branch was more severely affected. I shall not attempt to explain the discrepancies among the reports of various authors. Of these authors, Mahaim²⁶ has done the most careful and complete work. The fact that his conclusions uphold in the main the old terminology may be more a matter of interpretation of the lesions than of faulty technique.

The vascularization of the conduction system explains well why it is rare for one bundle branch alone to be affected.

The histopathologic study of the 6 cases reported in detail in this article shows that (1) bundle branch lesions are probably almost always bilateral, (2) the pathogenic factor is mainly disease of the coronary arteries or strain resulting from hypertension, (3) the morbid anatomic feature is fibrosis, (4) the new terminology of bundle branch block is more nearly correct for man than the old one, although the designation

as to right or left must be admitted to apply only to the branch more seriously damaged, (5) right bundle branch block is probably usually due to rheumatic arteritis or myocarditis, and left bundle branch block is usually due to so-called degenerative cardiovascular renal disease, (6) a bundle branch need not be entirely destroyed at any level in order to cause retardation of the rate of conduction of the impulse through it, (7) the form of the electrocardiographic curve depends at least partly on the relativity of the degree of damage of the two branches and the extent and severity of involvement of the more diseased branch, and (8) increased amplitude is not necessary for the diagnosis of bundle branch block

There remain many questions yet unanswered in regard to bundle branch block the pathogenic factor in the various types of bundle branch block or intraventricular block, the importance and effect of the location of the damaged region of the branch or branches, the alteration of the curves indicative of branch block by the extent and severity of the myocardial disease, the degree of heart failure and the relative weights of the ventricles, the form of the ST component of the electrocardiogram, the reason for the direction of the complexes in lead II, and many others

SUMMARY AND CONCLUSIONS

A review of the essential literature concerning bundle branch block has been made

Sixteen cases of bundle branch block, with necropsy data, have been reported

Six cases of bundle branch block studied by means of serial sections through the conduction system have been reported

Bundle branch block is usually due to disease of the coronary arteries, either rheumatic or degenerative, or to hypertension resulting in strain of the left ventricle and impairment of the nutrition of the endocardium and bundle branch

Bundle branch block is usually associated with bilateral bundle branch lesions, although one branch is usually more seriously affected than the other and probably usually determines the essential form of the electrocardiographic curve

The newer, or American, terminology is more nearly correct for bundle branch block in man, although it must be admitted that whether right or left is used to modify the diagnosis of this conduction disturbance, the adjective merely indicates the branch more seriously affected

The uncommon form of bundle branch block, right bundle branch block, is probably usually due to rheumatic arteritis or rheumatic myocarditis

The common form of bundle branch block, left bundle branch block, is probably usually due to degenerative cardiovascular renal disease, meaning coronary arteriosclerosis or arterial hypertension or both.

A bundle branch need not be entirely destroyed at any level in order to produce electrocardiographic alterations that may be designated as typifying bundle branch block.

An increased amplitude of the ventricular complex is not essential to the electrocardiographic diagnosis of bundle branch block.

Any increase of the QRS interval beyond 0.1 second may indicate lesions of the bundle branches.

Many questions remain unanswered in regard to bundle branch block, and many careful histopathologic studies must be made before most of them can be answered.

Most of the photographs used to illustrate this article were made by Roy M. Reeve, chief photographer of the Army Medical Museum.

UNUSUAL REACTIONS OF PATIENTS WITH HYPERTENSION TO GLYCERYL TRINITRATE

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Hypertension has long intrigued physicians. Arteriosclerosis, a condition commonly associated with hypertension, has been extensively and profitably studied both clinically and pathologically. Histologic studies of patients with hypertension, however, have yielded but little information concerning the mechanism of this malady. The few anatomic changes that do occur are usually ascribed to the changes secondary to elevation of the blood pressure. It might be better to consider hypertension as a kinetic or an altered physiologic expression of a diseased condition. Experiments illustrating altered or abnormal responses to a known or standard stimulus might then give some insight into this changed vascular state.

Following this line of reasoning, studies were begun. First a standard procedure or test was necessary. The amyl nitrite test of Stieglitz¹ appeared to fulfil the requirements, and it was tried. A small pearl of amyl nitrite (0.3 cc) was crushed in a towel and held directly under the patient's nose. He was then told to take three or four deep breaths of the vapor, studies of the blood pressure were made at frequent intervals. In actual practice the test was easily made but was impossible to standardize. No 2 patients would have the same depth of respiration, in fact, in many cases the patient instinctively drew his head away from the crushed ampule or held his breath, factors that precluded the inhalation of a known concentration of amyl nitrite.

A tablet of glyceryl trinitrate was then placed directly under the tongue, thus insuring a more definite administration of the drug. After a few patients had been tested by this method, severe reactions, viz, nausea, vomiting, collapse and the involuntary passage of urine, were noted. They appeared so alarming that it was decided to study their nature and frequency.

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1 Stieglitz, E J. Arterial Hypertension. Evaluation of the Prognosis, Arch Int Med 46:227-235 (Aug) 1930

METHOD

Fifty patients with essential hypertension and hypertensive heart disease were chosen from the outpatient dispensary. None of them had ever been given any nitrites in the past. They were admitted to the hospital the evening before the test so that they had twenty hours of complete rest in bed. The remainder were taken directly from the dispensary and put at complete rest in a recumbent position until three successive blood pressure readings taken at five minute intervals were within 6 mm of mercury. This was called the basal blood pressure. It usually took from one-half to one hour to reach this low fixed level of blood pressure. All patients were given this preliminary period of rest and quiet before any test was performed. After one test was finished another rest period was given until a satisfactory blood pressure level was reached before the second test was begun.

The Hines-Brown cold water test² was first given. The patient's hand was immersed in water at 3 C for exactly one minute. Great care was taken in moving the basin containing the ice water mixture to and from the patient so as to minimize his muscular movements. Two blood pressure readings were taken while the hand was in the water, the first one thirty seconds after immersion and the other just before withdrawal. After the hand was removed from the water, estimations of the blood pressure were made every thirty seconds for three minutes and thereafter for ten minutes. At the end of this period the blood

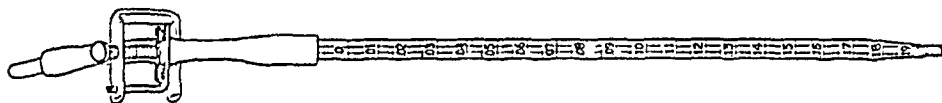


Fig 1—The capillary pipet which made possible the administration of accurate doses of spirit of glyceryl trinitrate

pressure had usually returned to its basal level. In those few in whom it had not, a short rest period restored basal conditions.

An alcoholic solution of glyceryl trinitrate (spirit of glyceryl trinitrate) was used in all experiments to avoid the uncertain and irregular absorption of the drug that followed the use of the tablets. It was given directly under the tongue by means of an accurately graduated pipet (fig 1). The glyceryl trinitrate content of the solution was assayed chemically by Dr Clarence W Muehlberger, Cook County toxicologist and toxicologist for the department of pharmacology of the University of Illinois College of Medicine, who also advised with us concerning this work. There were 82 mg of glyceryl trinitrate per cubic centimeter of solution. Except when actually used, this solution was kept in a glass-stoppered bottle in the refrigerator. Estimations of the blood pressure were made every half minute for ten minutes or until a fairly stationary level was reached. Subjective symptoms were recorded as they were mentioned by the patient, as were also the objective signs. Inferential questioning was avoided, since this might have colored some of the responses. Sixteen patients were given second and larger doses of the drug, and 4 were given third and still larger doses in an attempt to measure the quantitative responses of successive depressions in blood pressure.

² Hines, E A, and Brown, G E. The Cold Pressor Test for Measuring the Reactibility of the Blood Pressure. Data Concerning Five Hundred and Seventy-One Normal and Hypertensive Subjects, *Am Heart J* 11 1-9, 1936

Peripheral vasodilatation, the well known and typical nitrite reaction, led us to study the peripheral vascular changes. In 12 patients the finger plethysmograph of Johnson³ was used. Responses were quite variable. Capillary activity was investigated by means of a modification of the Lewis histamine flare method.⁴ Thirty-two patients were given 0.2 cc of a fresh 1:1,000 solution of histamine phosphate subcutaneously. Readings were made five, ten, fifteen and twenty minutes after the injections. Three fifths of the group (32 patients) were recalled, and their capillaries were studied by direct inspection of the nailfold both before and after the administration of glyceryl trinitrate.

RESULTS

Of this group of 50 patients with hypertension, 9, or 18 per cent, had mild to severe reactions after the administration of glyceryl trinitrate. These distressing responses to a drug that is generally considered quite harmless justify their full report.

REPORT OF CASES

CASE 1—E O, a white woman aged 68, had a basal blood pressure of 220 systolic and 120 diastolic. Four minutes after 0.24 mg ($\frac{1}{200}$ grain) of the standardized glyceryl trinitrate was placed under her tongue, the blood pressure fell to 170 systolic and 110 diastolic. A minute later the systolic reading was 70 mm, and six minutes after the drug was given the pressure could not be determined. She was unconscious and was covered with cold perspiration, and her skin was ashen gray. Syncope lasted for three minutes. Two minutes later the blood pressure was 106 systolic and 92 diastolic, she said she felt better than before she fainted, although she still had a slight feeling of impending death. Improvement gradually continued, so that twenty-two minutes after the drug was given she felt normal and the blood pressure was 124 systolic and 94 diastolic. Then she was told to move her arms and legs. Fifteen minutes after this exercise the blood pressure rose to 200 systolic and 118 diastolic (fig. 2).

CASE 2—W S, a white woman aged 68, had a basal blood pressure of 188 systolic and 122 diastolic. A slight fall in the blood pressure followed the giving of 0.4 mg ($\frac{1}{150}$ grain) of the standardized glyceryl trinitrate solution. Three minutes later the blood pressure had returned to the basal level, five minutes after the drug was given it was 208 systolic and 110 diastolic, but she felt ill, her face was gray and her skin was cold and clammy. She continued to feel ill, she tried to vomit and became unconscious for two minutes. Seven minutes after taking the glyceryl trinitrate she suddenly regained consciousness, her color became good and the blood pressure was 188 systolic and 84 diastolic. The recovery was complete within twelve minutes (fig. 3).

CASE 3—N G, a Negress aged 52, had a basal blood pressure of 224 systolic and 124 diastolic. About two minutes after 0.4 mg ($\frac{1}{150}$ grain) of the standard glyceryl trinitrate solution was given, this patient fell ill, was restless and tried to get out of bed. This disturbed the arm cuff so that consecutive readings were impossible, although the arm cuff was replaced as soon as possible. Five and a

3 Johnson, C A. Studies on Peripheral Vascular Phenomena. A New Device for a Study of Peripheral Vascular Phenomena in Health and Disease, Surg., Gynec. & Obst. **55** 731-737, 1932.

4 de Takáts, G. The Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, Arch. Int. Med. **48** 769-785 (Nov.) 1931.

half minutes after the drug was given, the blood pressure was 176 systolic and 106 diastolic, and she had a severe headache. During the next five minutes the blood pressure gradually fell to 128 systolic and 84 diastolic. Then she became ill, muttered incoherently, moaned feebly and tried to vomit. As the pressure fell

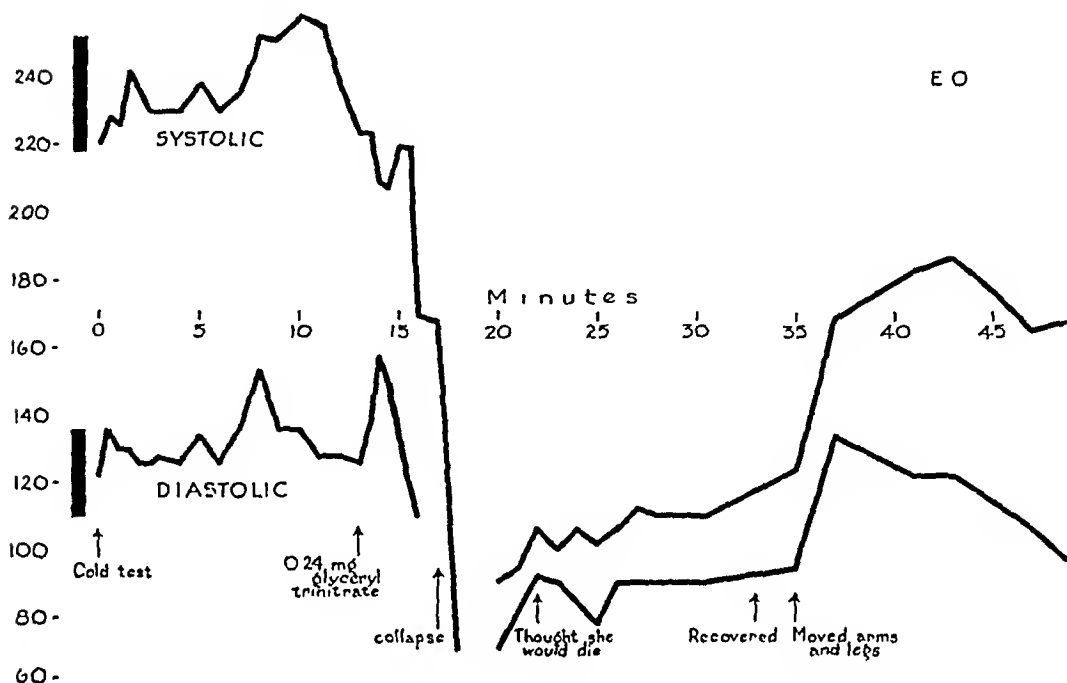


Fig 2 (case 1)—A marked fall in blood pressure occurred after 0.24 mg of glyceryl trinitrate was administered and a severe reaction occurred. The black blocks to the left represent the range of the patient's blood pressure before a basal level was reached.

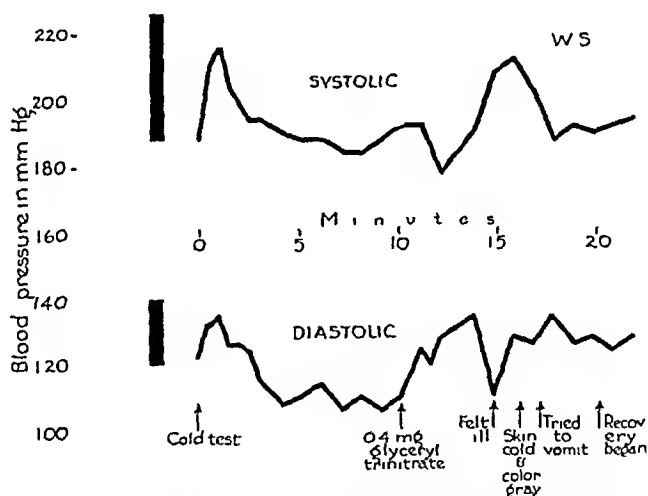


Fig 3 (case 2)—A slight rise in blood pressure and a severe reaction occurred after the administration of glyceryl trinitrate.

to its lowest point (118 systolic and 74 diastolic), the nausea disappeared, and the headache "wasn't bad." Inhalation of aromatic spirit of ammonia produced no rise in blood pressure, whereas movements of the arms and legs caused a marked increase (fig 4).

CASE 4—I B N, a 57 year old white woman, had a basal blood pressure of 176 systolic and 106 diastolic. She was given 0.4 mg ($\frac{1}{150}$ grain) of the standard glyceryl trinitrate solution. Three minutes later the blood pressure fell to 134 systolic and 112 diastolic, its lowest value, then it gradually rose

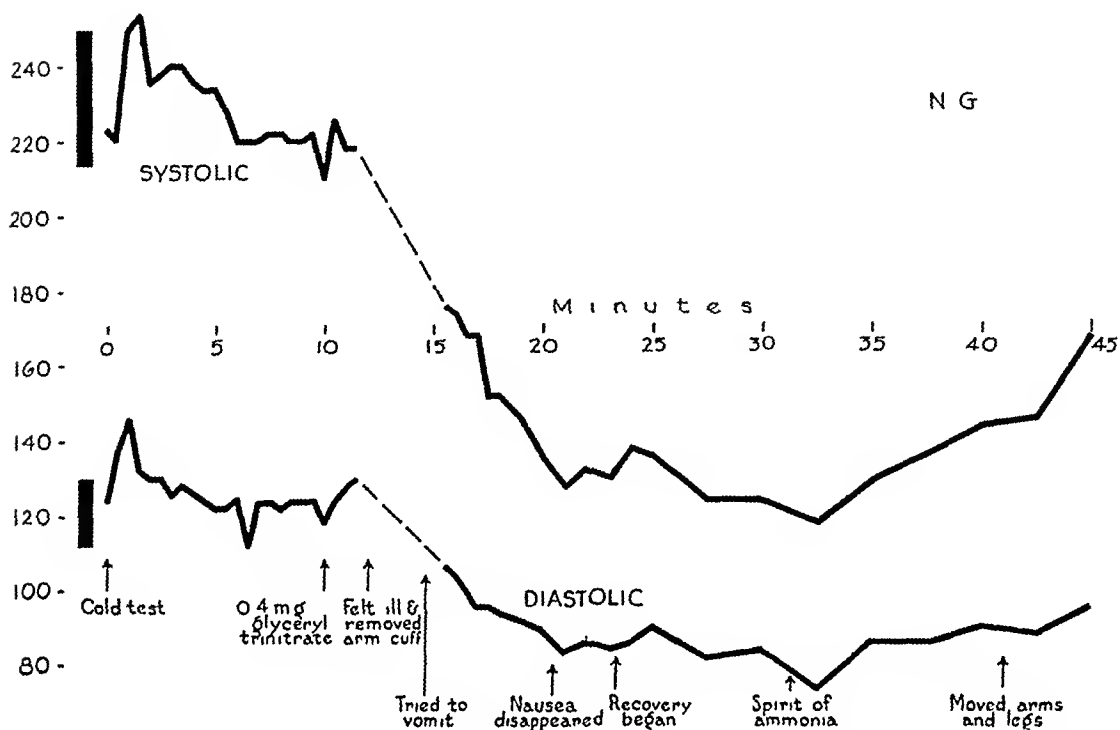


Fig 4 (case 3)—A fall in blood pressure and a severe reaction typical of the effects of nitrites occurred

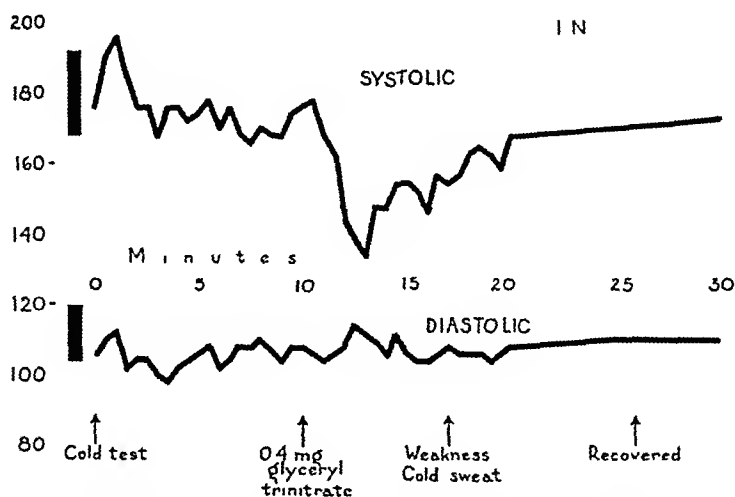


Fig 5 (case 4)—A mild reaction and no appreciable alteration of blood pressure were noted after the administration of glyceryl trinitrate

Seven minutes after the test was begun she complained of severe throbbing in the epigastric area, fulness in the region of the liver, headache and dizziness. Subsequently, she became extremely weak, perspired profusely and was soon covered with a cold sweat, however, her pulse was full and bounding. Within five minutes there was rapid and complete recovery. A second dose of 0.65 mg

($\frac{1}{100}$ grain) of glyceryl trinitrate was given. Although there was a lower and a more sustained fall in blood pressure, scarcely any symptoms were present except the abdominal pulsation.

CASE 5—M W, a white woman aged 45, had a basal blood pressure of 250 systolic and 120 diastolic. A tablet of glyceryl trinitrate, 0.6 mg ($\frac{1}{100}$ grain), was placed under her tongue, and seven minutes later she complained of faintness and nausea. Shortly afterward she became unconscious and made repeated retching and vomiting movements, succeeding in bringing up only a small quantity of bile-tinged mucus. During this time, about five minutes, she was ashen gray and had shallow respirations and cold, moist skin. Urine was passed involuntarily. Artificial respiration and spirit of ammonia were used to revive her. After twenty minutes she recovered completely, and an hour later she was induced to take 0.2 mg ($\frac{1}{100}$ grain) of glyceryl trinitrate. A slight headache was the only effect of this second dose of the drug.

CASE 6—E F, a 47 year old white man, had a basal blood pressure of 150 systolic and 90 diastolic. Seven minutes after a tablet of glyceryl trinitrate, 0.6 mg ($\frac{1}{100}$ grain), was given to him, he complained of being dizzy, mumbled a few words about approaching illness and fell forward from his chair. The syncopal attack lasted for three minutes, when he suddenly opened his eyes and asked what had happened. There was complete recovery fifteen minutes after the drug was given.

CASE 7—J L, a 47 year old white man, with a basal blood pressure of 160 systolic and 95 diastolic, was given a tablet of glyceryl trinitrate, 0.4 mg ($\frac{1}{150}$ grain), and seven minutes later he complained of vertigo, pounding in his head and nausea. He raised a small amount of bile-tinged vomitus but within twenty minutes had recovered completely.

CASE 8—A T, a white woman aged 51, with a basal blood pressure of 198 systolic and 115 diastolic, had been tested with 0.4 mg ($\frac{1}{150}$ grain) of glyceryl trinitrate previously and had suffered only slight throbbing in the head. She was recalled to the laboratory and given 0.4 mg ($\frac{1}{150}$ grain) of the drug preparatory to a study of changes in the capillary bed of the nail fold. Cyanosis, nausea and fainting occurred seven minutes after the drug was given. During this interval there had been a period of increased capillary flow, followed by the appearance of more capillary loops per field of observation. It was followed by a cessation of flow through the capillaries, and for fully two minutes before the reaction occurred there was cessation of flow through the capillary loops. Her symptoms were so alarming that several injections of 0.5 cc of 1:1,000 epinephrine hydrochloride had to be given. She soon regained consciousness and felt better. Eight minutes later, or fifteen minutes after the glyceryl trinitrate was given, the blood pressure was 115 systolic and 74 diastolic. Complete recovery speedily followed.

CASE 9—S H, a white woman aged 39, had a basal blood pressure of 220 systolic and 110 diastolic. She had previously been tested with 0.4 mg ($\frac{1}{150}$ grain) of glyceryl trinitrate but showed no reaction. Four minutes after she was given 0.2 mg of the standardized glyceryl trinitrate solution, she felt "funny." A few seconds later she slumped forward in her chair, and at five minutes the blood pressure was 230 systolic and 124 diastolic. Within the next three minutes two fields of capillaries in her nailfold were found to be inactive. Attention was then turned to reviving the patient. Although inhalations of spirit of ammonia did not appear to raise the systemic blood pressure, it did hasten her recovery. Ten minutes after the onset of this reaction there was a slight activity of the capil-

lary bed Recovery was well advanced by thirteen minutes after the collapse, the blood pressure was 218 systolic and 112 diastolic and normal capillary activity had been resumed

Sixteen patients were given a second dose of glyceryl trinitrate, and 4 of them were given a third dose of the drug This group were selected from the 50 because they showed a fall in blood pressure that was fairly typical of a nitrite reaction, but they did not give any reactions The blood pressure readings of this group averaged 220, an initial average dose of 0.4 mg ($\frac{1}{150}$ grain) of glyceryl trinitrate produced an average fall of 21 mm in the systolic pressure, an average second dose of 0.6 mg ($\frac{1}{100}$ grain) produced an average fall of 16 mm and the 4 patients who received a third dose of the drug showed about the same depression of blood pressure as that after the second dose

Posture appeared to affect the appearance of these reactions The more severe reactions occurred when the patient was tested while in a sitting position (cases 5 to 9), and less severe reactions took place while he was in a recumbent position (cases 1 to 4) Also in several cases the patient who had a mild reaction while in a prone position showed a slight secondary reaction when he got up from the examining table This could not be ascribed to muscular activity, since we frequently had each patient who had had such a reaction exercise his arms and legs after he recovered from his reaction but while he was still on the table No secondary reaction was ever observed after this type of exercise

A wide variety of responses followed the application of the Hines-Brown cold pressor test A rise of from 0 to 9 mm in systolic blood pressure occurred in 9 cases, a rise of from 10 to 19 mm in 13 cases and a lowering of 24 mm in blood pressure in 1 case Twenty patients, or 40 per cent of this group, showed a normal response, 14 patients, or 28 per cent, showed a preorganic hypertensive response, and 12 patients, or 24 per cent, showed an organic hypertensive response Seven of the 9 patients who had a severe reaction were given the pressor test Unfortunately we were unable to obtain readings for the other 2 (cases 5 and 6) Maximal systolic rises were 22, 28, 32, 20, 12, 12 and 0 mm No correlation between the height of the rise after the cold water test and the severity of the reaction after the giving of glyceryl trinitrate was possible In fact, earlier tests usually gave greater elevations of blood pressure than later ones This was due to the increasingly greater care that was taken to minimize the muscular movement of the patient In later experiments the patient's hand was passively placed in the basin of ice water that had been brought to his bedside

Tracings of arterial pulse waves, taken with the Johnson plethysmograph, showed no regular or typical reactions to glyceryl trinitrate, on the contrary, many of the patients showed a diminution or absence

of pulse waves Neither was the histamine flare test of any value, as a great majority of the patients tested showed normal responses There was no constant association of the size or the type of wheal, the area of erythema, the extent of the hypertension or the degree of tortuosity of the vessels It appears that the capillary damage must be severe before the histamine reaction is impaired

Studies of the capillaries were also made for the same 32 patients who were given the histamine test The nailfold was used, and five to ten minutes was spent in an initial study of capillary activity While the patient's hand was still in position under the microscope, 0.2 mg ($\frac{1}{260}$ grain) of the standardized solution of glyceryl trinitrate was placed under his tongue Observation of the capillary field was almost constant save for this slight interruption In the majority of cases there was an increased rate of flow through the capillaries of the skin several minutes after the drug was given, unaccompanied by any change in size of either the arterial or the venous limb After ten to fifteen minutes the flow returned to normal In 3 cases a decreased rate of flow followed the taking of the drug In only a few cases (4 patients) did complete blanching, i e., disappearance of the vessel, occur More commonly there would be a decrease in capillary flow, then the cells remained stationary in the vessel and blanching was not present Here and there a space would appear behind the mass of cells on the arterial side, and the cells would proceed through the venous limb, thus emptying the vessels

Another interesting observation was the simultaneous reaction of pairs of capillary loops In some fields these paired vessels could be easily detected by their synchronous acceleration, slowing and cessation of blood flow in contrast to the other capillaries that did not present identical variations Some of these paired vessels could be traced to a single common arteriole, a more deeply embedded vessel

COMMENT

Inhalation of amyl nitrite for the relief of pain in angina pectoris was first advocated by Lauder Brunton, in 1867 Since that time glyceryl trinitrate has been recommended for more than forty-six ailments⁵ At present, however, its usage is restricted mainly to hypertension and angina pectoris Its use has been suggested for seasickness,⁶

5 Merck, E Nitrite und Nitroverbindungen Wissenschaftliche Abhandlungen aus den Gebieten der Pharmakotherapie, Pharmazie und verwandter Disziplinen, Darmstadt, E Merck Chemische Fabrik, 1920, no 38

6 Percy, J F, and Hayden, D B Preliminary Report on Sodium Nitrite Therapy in Seasickness, J A M A 90 1193 (April 14) 1928

thromboangitis obliterans,⁷ cyanide poisoning,⁸ acrocyanosis⁹ and spasmodic conditions of the stomach and colon,¹⁰ as the result of favorable experimental evidence. Recently, it has been effectively employed for the relief of pain and colic after cholecystectomy by McGowan, Butsch and Walters¹¹

There is a prevailing opinion among the members of the medical profession that glyceryl trinitrate is harmless. Stieglitz¹ has said "The frequency with which amyl nitrite or nitroglycerine are administered with impunity in angina pectoris indicates strongly that the risk is minor if it exists at all." Unpleasant and even alarming symptoms had been recognized by the earlier writers, but the doses of glyceryl trinitrate were of the order of 6 mg ($\frac{1}{10}$ grain). The fatal cases of nitrite poisoning followed the ingestion, either accidental or intentional, of large quantities of the drug. Nystrom¹² described 2 cases of glyceryl trinitrate poisoning. At the end of an hour, cyanosis, dyspnea and delirium were present, coma and death followed within six hours. Necropsy showed marked filling of the vessels of the pia mater, venous sinus and cerebral cortex and injection of the optic thalamus and the ventricles. The kidneys and mucosa of the stomach, duodenum and colon were hyperemic, while the heart and lungs were normal. The normal appearance of the lungs was in keeping with the experimental results of Love and McGuigan,¹³ who found strips of the pulmonary artery unaffected by glyceryl trinitrate.

The exact lethal dose of glyceryl trinitrate for man has not been determined for want of reliable observations. In many reports, mention is made of the fact that part of the drug had been lost by emesis prior to absorption, making definite deductions impossible.

In Germany glyceryl trinitrate has been used extensively. It was for awhile in favor, only to fall into disuse. Neither lack of experience nor improper preparations of the drug could be blamed, but it was felt that the drug was highly poisonous and too dangerous. This period was followed by a number of reports which showed that the toxicity

7 Schlesinger, H. Die Prognose der Thromboangitis Obliterans, *Klin Wchnschr* **9** 2112-2114, 1930.

8 Hanzlik, P. J., and Richardson, A. P. Cyanide Antidotes, *J. A. M. A.* **102** 1740-1745 (May 26) 1934.

9 Cortés, C. Intermittent Claudication. Treatment, abstracted, *J. A. M. A.* **91** 917 (Sept 22) 1928.

10 Beams, A. J. Nitrites in Spasmodic Conditions of the Gastro-Intestinal Tract, *J. A. M. A.* **97** 907-910 (Sept 26) 1931.

11 McGowan, J. M., Butsch, W. L., and Walters, W. Pressure in the Common Bile Duct of Man, *J. A. M. A.* **106** 2227-2230 (June 27) 1936.

12 Nystrom, C. Om nitroglycerin, *Upsala lakaref. forh.* **2** 232-252, 1886.

13 Love, G. R., and McGuigan, H. A. The Action of Nitrites on Pulmonary Circulation, *J. Lab. & Clin. Med.* **10** 882-884, 1925.

of the drug was not great. As much as 0.30 to 0.4 Gm (5 to 7 grains) of glyceryl trinitrate was given to patients as a single dose without ill effect.¹⁴ Again glyceryl trinitrate was in vogue, and its popular use in hypertension and angina was general.

Increased sensitivity to the drug has been infrequently mentioned. Amyot¹⁵ reported on a patient who lost consciousness after contact with a piece of wood dipped in 1 per cent solution of glyceryl trinitrate. Two cases of collapse following the use of 0.65 mg ($\frac{1}{100}$ grain) of the drug were described by P. D. White.¹⁶ In a series of 110 patients receiving therapeutic doses of glyceryl trinitrate, 0.65 to 1.3 mg ($\frac{1}{100}$ to $\frac{1}{50}$ grain), four reactions were noted by Proger and Ayman.¹⁷ All these reactions occurred in women between the ages of 58 and 67 who had hypertension. In each instance a rapid and marked drop in blood pressure, decreased radial pulse, cold perspiration, weakness, anxiety, restlessness and pallor were noted. All presented the picture of impending collapse. In 2 cases the blood pressure was so low that it could not be recorded. During an attack, complete heart block was demonstrated electrocardiographically in 1 case. Collapse following the administration of glyceryl trinitrate occurred in 3 cases reported by Sprague and White.¹⁸ A therapeutic dose of the drug was presumed to have been given 1 man, but he had vomited and was unconscious when first seen. A 68 year old woman was given 0.3 mg ($\frac{1}{200}$ grain) of the drug for the relief of an anginal attack. Five minutes later she walked out of the room, but ten minutes later she tottered back and fainted. In the remaining case faintness, a small pulse, weak heart tones, ashen gray pallor and collapse were noted.

The serious nature of these reactions to therapeutic doses of glyceryl trinitrate led us to study their frequency and to seek a method of predicting their occurrence. As these reactions are similar to those of vasomotor collapse, it was thought that some method of testing vasomotor lability might give a clue to their nature. The cold water pressor test appeared to be suitable. Incident to the employment of this test, certain objections appeared. It was noted that the degree of movement

14 Stewart, D. D. Tolerance to Nitroglycerin, *J. A. M. A.* **44** 1678-1679 (May 27) 1905. Hochhaus, H. Discussion über Arteriosklerose, *Verhandl. d. deutsch. Cong. f. inn. Med.* **22** 165-166, 1904. von Noorden, C. Discussion über Arteriosklerose, *ibid.* **21** 152-154, 1904.

15 Amyot, cited by Merck.⁵

16 White, P. D. The Significance and Treatment of Cardiac Symptoms, *New England J. Med.* **205** 907-914, 1931.

17 Proger, S. H., and Ayman, D. Harmful Effects of Nitroglycerin, with Special Reference to Coronary Thrombosis, *Am. J. M. Sc.* **184** 480-491, 1932.

18 Sprague, H. B., and White, P. D. Nitroglycerin Collapse—A Potential Danger in Therapy. A Report of Three Cases, *M. Clin. North America* **16** 895-898, 1933.

incident to that made by the patient when immersing his hand in water seemed to be reflected in the rise in blood pressure. The test was modified so that the basin of ice water was moved to the patient's hand and his hand passively moved into and from the ice water, minimizing the muscular movements. Considerably less pressor effect occurred after this new procedure was instituted. In other experiments the hand was kept in the ice water mixture for longer periods, some patients had ice applied directly to the dorsum of the hand. However, the response to cold seemed in no way to bear a relation to the previous degree of arterial tension, rather, it appeared to be proportional to the discomfort of the patient. Similar observations have been reported by Pickering and Kissin¹⁹

Neither the histamine flare test nor the records of the pulse volume were of assistance in foretelling these reactions. Injection of histamine produces dilatation of the capillaries and venules of the skin. Using the Capps method²⁰ of measuring the tone of finer vessels, Wilkins, Haynes and Weiss²¹ found the tone of the arterioles normal even during collapse induced with sodium nitrite. The Johnson finger plethysmograph presumably records changes in the pulse volume in the smaller arteries or arterioles. Our tracings from this apparatus gave no information concerning these reactions.

Reactions have been attributed to the sudden fall in blood pressure, however, we noted mild reactions with an elevation of blood pressure. A rise in systemic blood pressure after the administration of glyceryl trinitrate is not uncommon²². Burgess²³ found that the reaction to nitrites was not related to the degree or the rate of fall of the blood pressure. This was also our experience. Wilkins, Haynes and Weiss have placed the site of action of the nitrites on the venous side of the circulation. This action results in an increase in the venous volume, a pooling of peripheral blood in the venous system and a decrease in

19 Pickering, G. W., and Kissin, M. The Effects of Adrenaline and of Cold on the Blood Pressure in Human Hypertension, *Clin. Sc.* **2** 201-207, 1936.

20 Capps, R. B. A Method for Measuring Tone and Reflex Constriction of the Capillaries, Venules and Veins of the Human Hand with the Results in Normal and Diseased States, *J. Clin. Investigation* **15** 229-239, 1936.

21 Wilkins, R. W., Haynes, F. W., and Weiss, S. The Role of the Venous System in Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* **16** 85-91, 1937.

22 Loomis, H. P. The Limitations of the value of Nitroglycerine as a Therapeutic Agent, *M. Rec.* **67** 411-413, 1905. Hewlett, A. W. The Effect of Amyl Nitrite Inhalations upon the Blood Pressure in Man, *J. M. Research* **15** 383-393, 1906. MacNider, W. de B. The Action of Nitrites on the Heart, *Am. J. M. Sc.* **135** 99-105, 1908. Dmitrenko, L. F. Zur Pharmakodynamik des Nitroglycerins, *Ztschr. f. klin. Med.* **68** 458-470, 1909.

23 Burgess, A. M. The Reaction to Nitrites in the Anginal Syndrome and Arterial Hypertension, *Ann. Int. Med.* **5** 441-462, 1931.

the volume of circulating blood. We found that deep breathing and movements of the arms and legs, procedures that facilitate the return of venous blood to the heart, were most effective in preventing collapse. Inhalation of spirit of ammonia and artificial respiration were more reliable than injections of epinephrine in preventing reactions and in resuscitating these patients. Also these reactions are less severe when the patient is in a prone position than when he is upright. Any procedure that will prevent venous blood from pooling or accumulating in the venous channels and will thus decrease the volume of effective circulating venous blood will prevent or minimize these reactions.

SUMMARY

Severe reactions not infrequently follow the administration of glyceryl trinitrate to patients with hypertension. The nature and frequency of these reactions were studied. Fifty patients with essential hypertension or hypertensive heart disease were selected from the outpatient dispensary. A chemically assayed solution of glyceryl trinitrate was carefully administered directly under the patient's tongue with an accurately graduated pipet. All tests were made under standard basal conditions, and frequent blood pressure readings were made. Nine patients (18 per cent) showed reactions, i. e., nausea, vomiting, syncope, collapse and involuntary passage of urine and feces. These followed doses as low as 0.24 mg. ($\frac{1}{100}$ grain) and were more severe when the patient was sitting up than when he was recumbent. All the patients recovered completely within an hour. Four well known clinical procedures were applied in these cases in the hope of determining unusual vasomotor lability. The Hines-Brown test, the histamine flare test, changes in the pulse volume and observations of the capillaries of the skin were of no assistance in predicting these reactions.

1853 West Polk Street

ACUTE AND CHRONIC MEDIASTINITIS

A STUDY OF SIXTY CASES

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BOSTON

Acute and chronic infections of the mediastinum are of sufficient frequency and importance to deserve more attention than has been given them. This seems especially significant since with the development and improvement of surgical technic it is possible in many cases to bring about striking improvement and even complete cure. During the past few years I have had the opportunity of observing a group of patients with various types of mediastinitis, and at this time I wish to review this experience and report on other patients who have been observed at the Boston City Hospital.

PATHOGENESIS OF MEDIASTINITIS

Infection of the mediastinal tissues is always secondary to infection of the various structures of the mediastinum or to infection extending to the mediastinal tissues from other locations, such as the neck, spine, lungs, pleurae or abdomen. The paths of extension of foci of infection in the neck and mediastinum have been made the subject of special study and investigation recently by Lerche,¹ Lambert and Berry,² Furstenberg and Yglesias,³ and Collier and Yglesias.⁴ For purposes of discussion, abscesses of the mediastinum can be divided into those involving the anterior mediastinum and those involving the posterior mediastinum. In some cases of rapidly advancing infection the entire mediastinum is involved, and a localized abscess does not appear. This condition is frequently referred to as diffuse phlegmonous mediastinitis. The present

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School

1 Lerche, W. Infected Mediastinal Lymph Nodes as a Source of Mediastinitis, *Arch Surg* **14** 285 (Jan) 1927, Suppuration in the Posterior Mediastinum, *ibid* **8** 247 (Jan) 1924

2 Lambert, A. V. S., and Berry, F. B. The Mediastinum. Paths of Extension of Infection from Focus in Mediastinum, *Arch Surg* **14** 261 (Jan) 1927

3 Furstenberg, A. C., and Yglesias, L. A Clinical Study with Practical Anatomic Considerations of Neck and Mediastinum, *Arch Otolaryng* **25** 539 (May) 1937

4 Collier, F. A., and Yglesias, L. The Relation of the Spread of Infection to Fascial Planes in the Neck and Thorax, *Surgery* **1** 323, 1937

group of sixty patients were divided in accordance with the location of the process, as shown in the accompanying table

Before discussing the cases it is well to review the paths of extension and the roentgenographic appearance in mediastinal infections. Familiarity with these two aspects of the condition is of great assistance in making a diagnosis

Data Concerning Sixty Cases of Acute and Chronic Mediastinitis

	Total Cases	Recovery	Death
A Abscess of anterior mediastinum			
I Acute abscess depending on			
a Osteomyelitis of sternum	1		1
b Ulceration of larynx	4		4
c Cellulitis of neck	2	2	
d Infarct of lung	1		1
e Pneumococcal infection	1	1	
Total	9	3	6
II Chronic mediastinitis from			
a Syphilitic mediastinitis	3	1	2
1 Tracheal stenosis, thrombosis of left innominate veins			
2 Thrombosis of superior vena cava			
3 Aneurysm of aorta, thrombosis of innominate veins			
b Mediastinopericarditis			
1 Syphilis with aneurysm of aorta	1		1
2 Rheumatic heart disease with mitral stenosis	1		3
c Cause undetermined	2	1	1
Total	9	2	7
B Abscess of posterior mediastinum			
I Acute abscess			
a Perforation of esophagus by			
1 Foreign body	9	3	6
2 Carcinoma of esophagus	7		7
3 Aneurysm of aorta	2		2
4 Stricture of esophagus	1		1
5 Rupture of esophagus	1		1
6 Tumor of lung	1		1
b Suppuration of lymph nodes	2	2	
Total	23	5	18
II Chronic abscess			
a Abscess, tuberculosis	3	2	1
C Acute diffuse mediastinitis			
I Pneumonia	14		14
II Peritonitis	2		2
Total	16		16
Total	60	12	48

PATHS OF EXTENSION IN MEDIASTINAL INFECTIONS

The diagnosis of a mediastinal abscess may depend, in part at least on the manner in which the infection spreads. Indeed, in some cases the diagnosis may be obscured by the presence of an infection in an area adjacent to the mediastinum. As previously stated, the pathways of spread have been worked out by Lambert and Berry² and Furstenberg and Yglesias.³ Lambert and Berry have pointed out that an abscess may spread upward into the fascial planes of the neck, downward into

the retroperitoneal connective tissue, posteriorly along the bodies of the vertebrae to the endothoracic fascia outside the pleura and the parietal pleura or through the broad ligaments of the lung beneath the visceral pleura and into the substance of the lung down the larger branches of the bronchial tree. An exudate in the anterior mediastinum dissects beneath the sternum and outside the anterior pleural reflexion. The abscess may also compress the esophagus or the trachea and bronchi and may actually rupture through these structures. Extension to the pleural cavity has also been observed.

ROENTGENOGRAPHIC APPEARANCE IN MEDIASTINAL INFECTIONS

Roentgen examination of the chest is of significance in the diagnosis of an abscess or of a chronic infection of the mediastinum. The changes consist of unilateral or bilateral triangular shadows superimposed on the cardiac shadow or of rounded or triangular shadows in the superior mediastinum. There may be, of course, an associated empyema or extrapleural abscess obscuring the pulmonary fields. When the abscess is in the superior mediastinum, the esophagus is displaced anteriorly. This can be seen under the fluoroscope, especially in the lateral view. When the abscess is lateral to the trachea, there is a unilateral rounded shadow, but the trachea is often not displaced. If a large abscess is near the bifurcation of the trachea, there may be some widening and compression of the bronchi, with pulmonary atelectasis.

The spine should be examined for signs of destruction in all cases of suspected posterior mediastinal abscess, since destruction is evidence of Pott's disease or of pyogenic or mycotic infection of the vertebrae.

The condition that is most likely to be confused with mediastinitis is a mediastinal pleural effusion or a mediastinal tumor.

In cases of mediastinal pleural effusion the shadows are triangular on either side of and continuous with the median shadows of the chest. No cardiac pulsation is seen in the abnormal shadow, and the heart or the lung may be displaced to the opposite side. The condition is almost always unilateral. In cases of paravertebral abscess the shadow is definitely separated from the posterior mediastinal pleural space and has its origin in the posterior thoracic wall. The shadow of the abscess is seen on both sides of the spine.

DIAGNOSIS

The diagnosis, then, will depend on the history of a condition which is capable of causing infection of the mediastinum, together with the symptoms and signs of infection of the mediastinum, familiarity with the paths of extension of such an infection, and the roentgenographic findings in the chest.

The roentgenographic findings in cases of chronic fibrous mediastinitis will vary, depending on the extent of the process and whether the pericardium is involved at the same time. In some cases there may be only a dense shadow extending beyond the costosternal borders or the hilus, irregular in outline, and not having the sharp, well defined borders of an abscess or tumor. The process is most conspicuous about the trachea and bronchi and extends to the central part of the lungs. During inspiration the heart is displaced upward.

ABSCESS IN THE ANTERIOR MEDIASTINUM

There were eight cases of abscess of the anterior mediastinum. Each abscess arose from an extension of an infection from the neck, larynx, sternum, lymph nodes or lung. In reports of one hundred and fifteen cases collected by Hare,⁵ abscess in the anterior mediastinum was more common than abscess in the posterior mediastinum. In many cases the abscess followed an injury, such as fracture of the sternum, or an infection, such as erysipelas or some condition involving the respiratory tract. Most of the chronic abscesses were due to tuberculosis. Infection of the wound after an operation on the neck may be followed by mediastinal abscess.

Another rare cause of abscess in the anterior mediastinum is an infection following an operation involving the upper portion of the abdomen, such as cholecystectomy, or an infection of the gallbladder without surgical treatment. Such cases have been recorded by Whipple⁶ and Kornblum and Osmond.⁷

When pus accumulates in the anterior mediastinum it tends to extend to the exterior, and it may present in the suprasternal notch or at the anterior border of the sternocleidomastoid muscle. It may gravitate down and cause a painful, tender area in the region of the xiphoid cartilage. On rare occasions such an abscess may present beneath the sternoclavicular region or may perforate into the costal interspaces in the parasternal line. An abscess which perforates is usually chronic and due to tuberculosis or actinomycosis.

The symptoms and signs of an abscess in the anterior mediastinum are those of an infection in this region. Pain is a conspicuous feature and is usually substernal and throbbing. There may be irritative phenomena, such as cough and pain on movement of the trachea. Swelling and edema of the neck and thoracic wall, with dilatation of the veins,

5 Hare, H. A. *Mediastinal Disease*, Philadelphia, P. Blakiston's Son & Co., 1888, p. 96.

6 Whipple, A. V., in discussion on Lambert and Berry.²

7 Kornblum, K., and Osmond, L. H. *Mediastinitis*, *Am. J. Roentgenol.* 32: 23, 1934.

may be conspicuous. In one case, after pneumonia which resolved spontaneously, there were signs of obstruction of the right innominate vein and swelling of the neck and right arm. Paroxysmal hypertension may accompany the abscess. Such a case was observed by McKinlay, Kinsella and Radl.⁸

On the whole, the signs of infection predominate, and the local signs may be indefinite, but when present they are due to compression and irritation of surrounding structures. Roentgenographic examination of the chest is important, since evidence of the presence of a supra-aortic structure which has displaced either the trachea or the esophagus posteriorly may be of great diagnostic assistance.

The following case illustrates the course of events when an abscess of the anterior mediastinum develops after an infection in the neck.

CASE 1—A 36 year old woman with symptoms of hyperthyroidism was admitted to the hospital, and thyroidectomy was performed. After the operation fever and signs of an infection in the operative wound developed. This condition persisted for fourteen days, when the temperature increased to 102 F. There were cough and a few rales in the left side of the chest posteriorly. A roentgenogram showed evidence of bronchopneumonia in the lower lobe of the left lung and some increase in the width of the shadow of the superior mediastinum. On the twentieth day after operation the temperature continued to be elevated, and the patient complained of severe substernal oppression, especially under the manubrium of the sternum. There was increased retromanubrial dullness, and the roentgenogram showed deviation of the trachea to the right, an increase in the supracardiac shadow and signs of consolidation of the lower lobe of the left lung. On the thirty-second day after the operation the wound in the neck was bulging somewhat, and roentgenograms continued to show widening of the mediastinum. A clamp was inserted into the superior mediastinum from the draining sinus in the neck, and a large amount of pus was evacuated. The pus showed hemolytic streptococci in pure culture.

After drainage of the abscess the temperature gradually declined, and the improvement was striking. Complete recovery followed within ten weeks after operation and within five weeks after drainage of the abscess. The course of the temperature is charted in figure 1.

Summary—This case illustrates the course of events when a mediastinal abscess follows an infection of the neck. The symptoms and signs of infection were conspicuous for several weeks before there was evidence suggesting a mediastinal abscess. After drainage of the abscess, recovery followed promptly.

CHRONIC ABSCESS OF THE ANTERIOR MEDIASTINUM

Chronic abscess of the anterior mediastinum is due most often to tuberculosis. Fibrosis of the anterior mediastinum is due to the same cause, but, in addition, one must consider the possibility of syphilis.

⁸ McKinlay, C. A., Kinsella, T. J., and Radl, R. B. Acute Essential Hypertension Precipitated by Mediastinal Abscess, *Arch Int Med* **54** 645 (Oct) 1934.

Tuberculous abscess of the anterior mediastinum results from broken-down necrotic lymph nodes or from an extension of tuberculosis from the sternum or the lung. It may remain localized, perforate the thoracic wall, appear in the suprasternal notch or produce sinuses through the thoracic wall. When sinuses appear the disease may be confused with perforation of an infected dermoid cyst of the mediastinum or with actinomycosis.

The symptoms and signs are those of chronic infection, with evidence by physical and roentgenologic examination of a mass in the anterior mediastinum causing compression of blood vessels or swelling of the thoracic wall. There were no instances of chronic tuberculous abscess in the present group of cases.

CHRONIC DIFFUSE MEDIASTITIS

Chronic fibrous mediastinitis arises in the same way as acute mediastinitis, but the etiology is somewhat different. It is caused by (1) tuberculosis, (2) syphilis, (3) mycotic infection (actinomycosis or

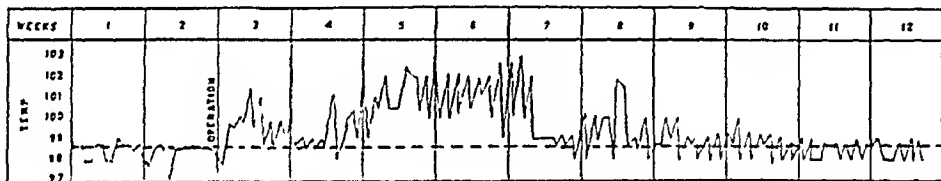


Fig 1 (case 1) —Chart showing the temperature curve in a case of mediastinitis following thyroidectomy

streptotricosis), (4) rheumatic fever, (5) pyogenic infection, (6) pneumoconiosis and (7) chronic paragonimiasis.

The diagnosis frequently depends on associated lesions of the lungs, bones, heart, aorta, pericardium or other mediastinal structures. When such signs are not cleancut, the commonest features are those of compression of the superior vena cava or of the innominate veins, without evidence of a tumor or aneurysm of the aorta, and there is a comparatively long duration of the symptoms and signs, with few constitutional symptoms. When there are, in addition, signs of bronchial or tracheal stenosis, paralysis of the recurrent laryngeal nerves or pericarditis, the extent of the lesion may be postulated, and the etiologic factor may be suggested.

In nine of the sixty cases there was chronic fibrous mediastinitis. Four were instances of mediastinopericarditis, in one case the condition was due to syphilis and was associated with aneurysm of the aorta, and in three cases it was due to rheumatic fever, with associated mitral stenosis. In three cases the condition was due to syphilis, in one case there was associated bronchial stenosis, with resultant thrombosis of the left innominate vein, in one case there was associated thrombosis

of the superior vena cava and in one case there were associated aneurysm of the aorta and thrombosis of the left innominate vein. The cause of the mediastinitis in the other two cases remained obscure.

The following case illustrates the sequence of events in one of the cases of syphilitic mediastinitis, with bronchial stenosis and thrombosis of the innominate veins.

CASE 2—A man aged 43 years complained of cough and swelling of the left arm. He had been well until one year before admission to the hospital, when there had developed a cough with expectoration of white mucoid sputum. He had dyspnea on exertion and at night, which was often relieved by expectoration. Two weeks before admission to the hospital he had some pain in the chest, it was substernal and radiated to the left axilla. He had noticed some swelling of the left arm.

Examination showed dilatation of the right jugular vein and swelling of the upper part of the left side of the chest and neck. The upper part of the left arm was swollen and edematous. All the signs of occlusion of the left internal jugular and of the left innominate vein were evident. There was no dilatation of the veins over the upper part of the chest. Examination of the heart revealed no abnormality. The retromanubrial dulness was not increased. The lungs were clear except for signs of partial obstruction of the bronchus leading to the upper lobe of the left lung, where there were high-pitched squeaking rales, suppression of the breath sounds and impaired resonance on percussion.

Roentgenograms showed no tumor mass in the superior mediastinum, and the aorta was of normal size and in normal position. There were increased shadows at the pulmonary roots, which were interpreted as being evidence of pulmonary fibrosis. Bronchoscopic examination showed narrowing and scarring of the left main bronchus but no tumor. The Wassermann reaction was positive. During observation the patient had two small pulmonary infarcts, which were diagnosed by the presence of cough, bloody expectoration, pain in the chest and a pleural friction rub.

Under antisyphilitic treatment he improved remarkably. The signs of vascular occlusion gradually diminished but did not subside. At the end of one year of observation he had gained weight and was greatly improved.

Summary—A man with syphilis showed signs of bronchial obstruction and occlusion of the left innominate and jugular veins, with several attacks of pulmonary infarction. Remarkable improvement followed antisyphilitic treatment.

While syphilis is an infrequent cause of diffuse mediastinitis, it may be associated with (1) an aneurysm of the aorta, (2) syphilitic tracheo-bronchial stenosis or (3) pericarditis, or (4) it may occur independent of these three lesions. In the cases in which syphilitic mediastinitis occurs independent of the first three conditions, the signs of occlusion of the superior vena cava or of the innominate vein predominate, since the anterior and the superior mediastinum are involved predominantly. Other structures that become constricted are nerves and large bronchi. The case reported by Knox⁹ is an excellent example of this type of

⁹ Knox, L. C. Chronic Mediastinitis, *Am J M Sc* **169** 807, 1925

mediastinal disease, and Martland¹⁰ has expressed the opinion that syphilis is one of the commonest causes of chronic mediastinitis.

In a recent review of the literature on thrombosis of the superior vena cava by Ochsner and Dixon,¹¹ it was reported that in no less than 19 per cent of the cases the condition resulted from syphilis and in 91 per cent of these syphilitic mediastinitis was the cause. In the other 10 per cent the condition was said to have resulted from phlebitis, and it is not unlikely that in many of these cases there was associated mediastinitis. In one of the cases listed in the accompanying table there was thrombosis of the superior vena cava, and in two others there occurred thrombosis of the innominate vein on the left side. In case 2 of the present series there was thrombosis of the innominate vein as well as an associated syphilitic lesion of the bronchus.

Examples of mediastinitis associated with syphilis of the trachea and bronchi were cited in Conner's¹² classic review of the subject. Usually the signs of an intrinsic lesion of the trachea or bronchi predominate, and occasionally palsy of the recurrent laryngeal nerve or occlusion of blood vessels occurs.

Cases of mediastinitis associated with aneurysm are not frequent, but in most instances the mediastinitis is localized about the root of the aorta. Sometimes, however, it is more diffuse and produces thrombosis of veins, as in one of the cases mentioned, or it is associated with pericarditis. These cases are discussed under the headings mediastinopericarditis.

MEDIASTINITIS ASSOCIATED WITH PERICARDITIS— MEDIASTINOPERICARDITIS

Under the heading mediastinopericarditis there is often described a group of cases in which there are signs of adherent pericardium as well as mediastinitis. In the present group there were four cases of chronic diffuse mediastinitis associated with chronic adhesive pericarditis. In one the mediastinitis was presumably the result of syphilis, since the condition was associated with an aneurysm of the arch of the aorta. In the other three cases the mediastinopericarditis was associated with mitral stenosis and probably resulted from a rheumatic infection. In all the clinical features were those of cardiac insufficiency with congestion.

10 Martland, H. S. Diseases of the Mediastinum. Certain Anatomical Considerations, in Diseases of the Respiratory Tract, Eighth Annual Graduate Fortnight of the New York Academy of Medicine, Philadelphia, W. B. Saunders Company, 1936, p. 365.

11 Ochsner, A., and Dixon, J. L. Superior Vena Caval Thrombosis. Review of the Literature and Report of Cases of Traumatic and Infectious Origin, *J. Thoracic Surg.* 5: 641, 1936.

12 Conner, L. A. Syphilis of Trachea and Bronchi, *Am. J. M. Sc.* 126: 57, 1903.

In the case of syphilis the signs of aneurysm of the aorta were associated with heart failure which had resulted from compression of the pulmonary artery and hypertrophy and dilatation of the right ventricle. The conspicuous feature of the heart failure was recurrent ascites. It is doubtful whether the adherent pericardium played any part in the circulatory failure since the heart was of normal size the pericardial adhesions were not thick and the cardiac muscle was not compressed. Similar cases of heart failure in aortic aneurysm have been recorded by Rohr and Ryffel¹³

In the three cases of valvular disease due to rheumatic fever there were pericardial adhesions as well as adhesions throughout the mediastinum. In these cases the clinical features were those of disease of the mitral valve and heart failure, and there was no good reason for believing that the pericardial adhesions were responsible for the heart failure. The venous congestion could have been caused by the heart failure and not by the compression of the veins by the mediastinal adhesions.

It is now admitted that the clinical features which have been described as being due to mediastinopericarditis can be reproduced by pericarditis alone (*concretio cordis*) in the absence of mediastinitis since removal of the thickened pericardium is followed by complete recovery in some cases. It also seems clear that mediastinopericarditis may be associated with valvular heart disease and in these cases it may be difficult to assess the relative importance of the valvular disease and the mediastinopericarditis in the production of the clinical picture. In some cases at least, the valvular defects seem to dominate the picture and the mediastinopericarditis is of little consequence so far as the symptoms and signs are concerned.

There are cases, however, in which both components of mediastinopericarditis are important, and these are generally cases of tuberculosis of the pericardium and mediastinum. For example, in the three cases of mediastinopericarditis described by Kussmaul¹⁴ there was tuberculosis not only of the pericardium but of the mediastinum as well. In all the cases there were signs of circulatory failure and of hemorrhagic pulmonary infarction.

It seems plain then that chronic fibrous mediastinitis may in itself produce the signs of venous congestion in the tributaries of the superior vena cava but when the signs of congestive heart failure are

13 Rohr, K. and Ryffel W. Ueber Einengungen und Verlegungen der Lungen Schlagader durch Aortenaneurysmen. Frankfurt Ztschr f Path 36.525, 1928

14 Kussmaul A. Ueber schwierige Mediastino-Pericarditis und den paradoxen Puls, Berl klin Wchnschr 10 433, 445 and 461, 1873

superimposed on this picture, the condition is due to involvement of the pericardium, compression of the pulmonary artery or an associated valvular disease. All these combinations may be observed. The involvement of both the pericardium and the mediastinum in cases of tuberculosis may explain in part the poor results of surgical treatment of tuberculosis of the pericardium when there is a clinical picture of *concretio cordis*.¹⁵

ABSCESS OF THE POSTERIOR MEDIASTINUM

Abscess in this region was more common than in the anterior space, the commonest causes being perforation of the esophagus and suppuration of lymph nodes. Other causes are extension of an infection from the retropharynx or from the spine. A rare cause is extension of infection from the lung, pleura or abdominal cavity.¹⁶ This abscess shows only a slight tendency to approach the surface, but it extends up and down the posterior mediastinum. For this reason it may become large before producing symptoms of pressure. It may rupture into the bronchi, trachea, esophagus or pleural cavity. Rarely it may point in one of the posterior triangles of the neck, or it may extend retroperitoneally and point in the groin. The symptoms of an abscess of the posterior mediastinum may be indecisive, since a large accumulation of fluid can occur without producing many symptoms. The common ones are pain and dysphagia or irritative symptoms, such as cough and dyspnea.

The pain is felt most often on swallowing and coughing, but it is generally between the shoulder blades and may radiate anteriorly along the course of the intercostal nerves. When the trachea is encroached on it may be painful for the patient to perform any movements that involve the trachea, such as coughing or swallowing. Swallowing is also difficult, owing to compression of the esophagus, especially in the upper part of the chest.

The physical signs may be few, and the only ones found will be dulness over the spinal processes posteriorly and increase of whispered and spoken words. The most reliable signs are brought out by roentgenographic examination, which shows a rounded shadow with sharp borders and a convex outline on the lateral surface, extending from the midportion of the chest. The esophagus is displaced ventrally and laterally, and there is often obstruction to the flow of barium sulfate through it.

¹⁵ Keefer, C. S. Tuberculosis of the Pericardium. A Study of Twenty Cases, *Ann Int Med* **10** 1085, 1937.

¹⁶ Auchinchloss, H., in discussion on Lambert and Berry.²

MEDIASTINAL ABSCESS FOLLOWING PERFORATION OF THE ESOPHAGUS

The commonest cause of posterior mediastinal abscess is perforation of the esophagus by a foreign body or a tumor. Rarer causes are compression necrosis from an aneurysm of the aorta or a tumor, rupture of the esophagus from vomiting¹⁷ or dilatation of a stricture and perforation of a diverticulum.

From the standpoint of treatment, perforation of the esophagus is important. It is most often due to swallowing a bone of a fish or fowl or some other sharp-pointed body, such as a tack, nail or pin.

The following two cases illustrate the course of events when a favorable outcome follows a mediastinal abscess resulting from perforation of the esophagus by a foreign body.

CASE 3—A young woman was admitted to the hospital complaining of swallowing a fish-bone, which was followed by pain in the upper part of the sternum and the left side of the back and by dysphagia. Examination showed nothing

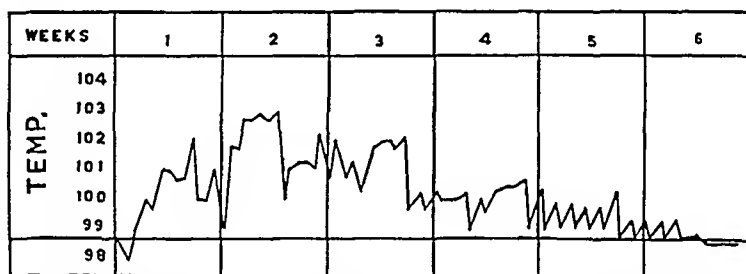


Fig 2 (case 3) —Chart showing the temperature curve in a case of mediastinitis following perforation of the esophagus by a foreign body

abnormal except that by fluoroscopic examination there was obstruction of the flow of barium in the upper part of the superior mediastinum.

The course of the illness was as follows. The temperature fluctuated, as shown in figure 2. During the first week the patient was extremely uncomfortable, the pain in the chest was severe, the temperature increased and the dysphagia and pain on swallowing increased. Roentgenographic examination showed an increased area of density in the superior mediastinum. On the seventh day of her illness she had an attack of retching which was followed by the vomiting of 6 ounces (175 cc) of bright red blood and pus. After this she continued to regurgitate some blood and pus. On the twelfth day of illness she had another attack of vomiting, raising several ounces of blood, mucus and pus. The temperature remained elevated for three more weeks, but during this time she improved progressively. She continued to expectorate moderate amounts of pus for four weeks. This stopped during the fifth week, and during the sixth week the temperature became normal, she felt well, a roentgenogram of the chest was normal and she returned home completely recovered.

¹⁷ Weiss, S, and Mallory, G K. Lesions of the Cardiac Orifice of the Stomach Produced by Vomiting, *J A M A* **98** 1353 (April 16) 1932. Mallory, G K, and Weiss, S. Hemorrhages from Lacerations of the Cardiac Orifice of the Stomach Due to Vomiting, *Am J M Sc* **178** 506, 1929.

Summary—A woman had a mediastinal abscess which developed after the swallowing of a fish-bone. Recovery followed the rupture of the abscess into the esophagus. The total duration of the illness was six weeks.

CASE 4—A woman aged 44 years stated when admitted to the hospital that she had swallowed a fish-bone two weeks previously. While eating fish she felt that a bone became lodged in her throat, since she immediately had a choking sensation and a feeling of discomfort. Examination soon after this happened failed to reveal a foreign body, either by laryngoscopic or bronchoscopic study. The symptoms of a choking sensation, difficulty in breathing and coughing continued and were associated with dysphagia.

Examination—When she was seen two weeks after the onset of her illness, she had fever, dysphagia, cough, with the expectoration of frothy sputum, and pain across the upper part of the right side of the chest anteriorly. Examination showed fever, tachycardia, leukocytosis (18,000 leukocytes) and signs of bron-

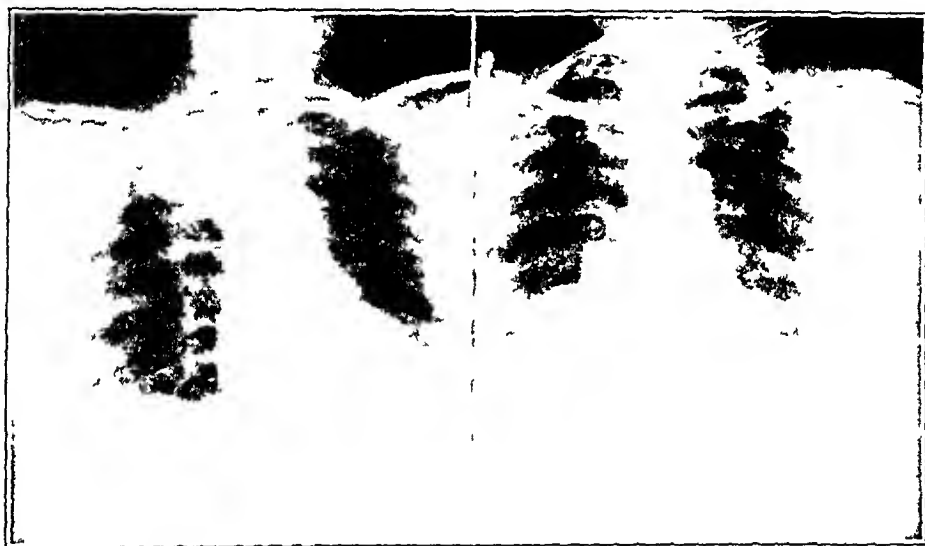


Fig 3 (case 4)—Roentgenograms made in a case of mediastinitis caused by a pulmonary abscess due to a foreign body. The first roentgenogram was taken the first week of observation and shows the shadow in the upper mediastinum and the upper lobe of the right lung. The second one was taken after recovery.

chopneumonia of the right lung. The left lung was clear. There was increased retromanubrial dulness, especially to the right. Fluoroscopic examination showed a large dense shadow in the superior mediastinum at the level of the first and second ribs which did not pulsate but moved slightly on coughing, not on swallowing. It was situated about midway between the anterior and the posterior wall of the chest. There was no displacement of the esophagus, but the trachea seemed to be displaced slightly to the right. The temperature chart is shown in figure 3.

Course—The patient's illness was of several months' duration, and during the first eight weeks of observation the course was as follows:

First Week. The patient had fever, tachycardia, cough and respiratory difficulty. There were many rales over the upper and lower lobes of the right lung. A roentgenogram showed a mass in the superior mediastinum and increased density of the upper lobe of the right lung as well as a triangular mediastinal

shadow extending to the right of the cardiac shadow. Moist rales were heard over the right lung posteriorly.

Second Week The temperature remained elevated. The signs at the base of the right lung were diminishing, and a roentgenogram showed a diminution of the size of the shadow at the cardiophrenic angle. The shadow in the upper lobe of the right lung was also diminishing in size.

Third Week The physical signs remained essentially the same as before, but a roentgenogram showed considerably more infiltration of the upper lobe and also of the lower lobe of the right lung. The cough increased in frequency and severity, the breath became foul and the sputum was more abundant and blood-streaked (fig 3).

Fourth Week During this week the temperature was lower, and the rales over the lower lobe of the right lung diminished, but the coarse rhonchi and dulness over the upper lobe of the right lung persisted. A roentgenogram showed a great decrease in the density of the upper lobe of the right lung. The right cardiophrenic angle showed some haziness, and the right dome of the diaphragm was higher than the left dome.



Fig 4 (case 4) —Chart showing the temperature curve. The white blood cell counts are recorded in thousands per cubic millimeter.

Fifth and Sixth Weeks Improvement continued, the signs in the lungs becoming fewer. Fluoroscopic examination at the beginning of the sixth week showed the trachea and esophagus pushed slightly to the left at the level of the first rib and some mottling of the apex of the right lung, with an increase in the linear markings extending from the pulmonary root toward the apex. The patient continued to complain of a foul breath, a bad taste and some pain in the right side of the chest, especially while lying on that side.

Seventh and Eighth Weeks The patient continued to improve but had pain and distress over the upper part of the chest. A roentgenogram showed the esophagus in normal position and no signs of fistula or obstruction. There continued to be a shadow in the superior mediastinum which was abnormally large. At the end of this period she was allowed to return to her home. She remained there four weeks and then returned to the hospital.

Twelfth Week For two weeks after leaving the hospital she felt greatly improved except for a continuation of the pain in the upper part of the right side of the chest anteriorly. Two weeks later the pain became more severe and spread across the upper part of the chest. It was a burning pain, often intermittent and not associated with cough or increased by respiratory effort. It was exaggerated when she was in a recumbent position. The examination revealed only diminished resonance over the upper lobe of the right lung. She was discharged again, after five days in the hospital.

First Year One year after she swallowed the fish-bone she reported that after a violent attack of coughing, which had been precipitated by the inhalation of smoke, she coughed up a large fish-bone. After this she remained well.

Summary—A woman swallowed a fish-bone, which caused a mediastinal abscess that perforated into the lung and drained. This healed entirely, and one year later, after a violent fit of coughing, the foreign body was dislodged. Complete recovery resulted.

This case illustrates what may happen after the perforation of the esophagus by a foreign body. There was evidence that the abscess had perforated the lung, producing pulmonary abscess, bronchopneumonia and physical signs. Roentgenographic examination indicated that the process was extensive also in the posterior mediastinum. It was striking that the signs of acute infection subsided after the healing of the pulmonary abscess and several months before the foreign body was recovered. This was an example of drainage of a mediastinal abscess after its rupture into the lung.

In addition to perforation of the esophagus by a foreign body, the most common cause is a neoplasm of the esophagus. I¹⁸ reviewed a group of these cases several years ago, including several in which mediastinitis was a feature.

A rarer form of suppurative mediastinitis arises from necrosis of the esophagus resulting from external pressure, especially that due to an aneurysm, a mediastinal tumor (usually a lymphosarcoma) or metastatic lymph nodes from the lung or esophagus. The following case illustrates the course in a case of mediastinal abscess due to erosion of the esophagus by an aneurysm.

CASE 5—A Negro aged 34 years complained of pain in the chest of one year's duration. Two weeks before admission to the hospital he had a severe constant boring pain in the chest, localized in the upper end of the sternum a few centimeters to the right of the midline. This was not exaggerated by respiratory effort, but it radiated into the middle of the back. It was constant day and night and prevented sleep. There was some cough, with expectoration of moderate amounts of sputum. He had syphilis fifteen years previously which had been treated inadequately.

The patient appeared uncomfortable. The temperature, pulse rate and respiratory rate were normal. The blood pressure was 150 systolic and 100 diastolic. There were a few rales at the base of the left lung posteriorly and a moderate increase in the retromanubrial dullness. The heart was of normal size, and the sounds were clear. The abdomen and extremities were normal. There was no anemia or leukocytosis, the Kahn and Hinton reactions were positive. Roentgenographic examination of the chest showed an enlarged aorta, an increase in the width of the mediastinal shadow and a fine mottling of the upper fields of both lungs, suggesting miliary tuberculosis (fig 5).

18 Keefer, C. S. Pleural and Pulmonary Complications of Carcinoma of the Esophagus, *Ann Int Med* 8 72, 1934.

The temperature varied from 98.6 to 100 F for three days and then remained normal until death occurred. The pulse and respiratory rates gradually increased from 80 to 140 per minute and from 20 to 40 per minute, respectively. On the day after entrance to the hospital he became nauseated, and from that time on he regurgitated and vomited everything taken by mouth. The day before death (eight days later) he vomited small amounts of blood and had great respiratory distress, with both inspiratory and expiratory wheezing. The right lung showed many moist rales, but the left lung was clear. The respiratory difficulty increased, and he died on the ninth day.

Necropsy showed syphilitic aortitis with an aneurysmic formation in the descending arch which had ruptured into the mediastinum and the right pleural cavity. The blood clot in the mediastinum had eroded the esophagus and had



Fig 5 (case 5) —Hematoma of the mediastinum following rupture of an aortic aneurysm

caused perforation and a mediastinal abscess. The right bronchus was also compressed. There was, in addition, miliary tuberculosis of the lungs, liver, spleen and kidney, with caseous tuberculosis of both adrenal glands.

It is clear that this young man had an aneurysm of the aorta which bled into the mediastinum and the right pleural cavity. The blood clot had caused necrosis of the esophagus with perforation and an abscess of the mediastinum. There was chronic miliary tuberculosis without constitutional signs of infection. This case illustrates, then, how a mediastinal abscess can arise from a perforation of the esophagus from external pressure due to a hematoma. Similar cases of hematoma of

the mediastinum in aneurysm of the aorta have been recorded by Lenk¹⁹ and myself¹⁸

MEDIASTINAL ABSCESS FOLLOWING SUPPURATION OF LYMPH NODES

This condition is most important, since the prognosis seems to be better than in cases in which abscess in this area arises in some other way. The abscess may be due to hemolytic streptococci or pneumococcal infections and most often follows as infection of the throat, lungs or bronchi. An abscess arising from the throat is most often retroesophageal or peritracheal. The following two cases illustrate (1) the result of an infection arising in the throat and (2) an infection following an attack of grip.

CASE 6—A man 46 years of age was admitted to the hospital on account of fever and sore throat. Five weeks previously he had an attack of coryza and tonsillitis which were not severe enough to confine him to bed. He continued with his daily work for two weeks, when he was forced to remain at home on account of chills, fever and difficult and painful swallowing. This was accompanied with attacks of coughing which was productive of mucopurulent sputum. During the third week of his illness the chills and fever continued, and the pain and difficulty in swallowing increased. In addition, he had some pain and discomfort about the base of the neck which radiated into the occiput during swallowing. The temperature gradually decreased, and he felt somewhat improved so far as the sore throat was concerned, but the dysphagia continued.

Physical Examination—Physical examination showed that the patient was acutely ill and pale. He had few complaints, but it was difficult for him to swallow liquids or solid foods. The temperature was 101.5 F. The throat was red, and the pharynx seemed edematous and swollen. Palpation of the pharynx failed to reveal any localized mass, although the mucous membrane was swollen. The lymph nodes of the neck were not enlarged, and the thyroid gland was not palpable. The trachea was in the midline and could be moved laterally without discomfort, it moved up and down on swallowing, but this caused some discomfort. There was no swelling of the neck or area of tenderness on deep pressure. The movements of the cervical portion of the spine did not seem limited in extent. Examination of the chest failed to show any abnormal areas of prominence, and the superficial veins of the thoracic wall and the jugular veins were not swollen. There was no retromanubrial dullness or displacement of the heart or mediastinum laterally. The lungs were clear throughout. The heart was in normal position, and the sounds were clear. Dullness extended from the first to the fourth dorsal vertebra, and over this area the whispered voice and the breath sounds were distinct and bronchial. Aside from these abnormalities there was nothing distinctly abnormal to be made out on physical examination of the chest.

The abdomen was soft, and no organs were palpable. The extremities, genitalia and reflexes were normal.

Laboratory Examination—The red blood cells numbered 3,860,000 per cubic millimeter, with 74 per cent (Sahli) hemoglobin. The white blood cells numbered 25,000 per cubic millimeter, with 85 per cent polymorphonuclear cells.

The urine was normal.

¹⁹ Lenk, R. Die Röntgendiagnostik der intrathorakalen Tumoren und ihre Differentialdiagnose, Vienna, Julius Springer, 1929, p. 357.

Roentgenographic examination showed the heart in normal position, the pulmonary fields were clear. In the superior mediastinum there was a bilateral rounded shadow with concave borders, slightly more prominent on the right side than the left. It was distinctly supra-aortic, and it had not displaced the trachea laterally or the aortic arch downward (fig 6)

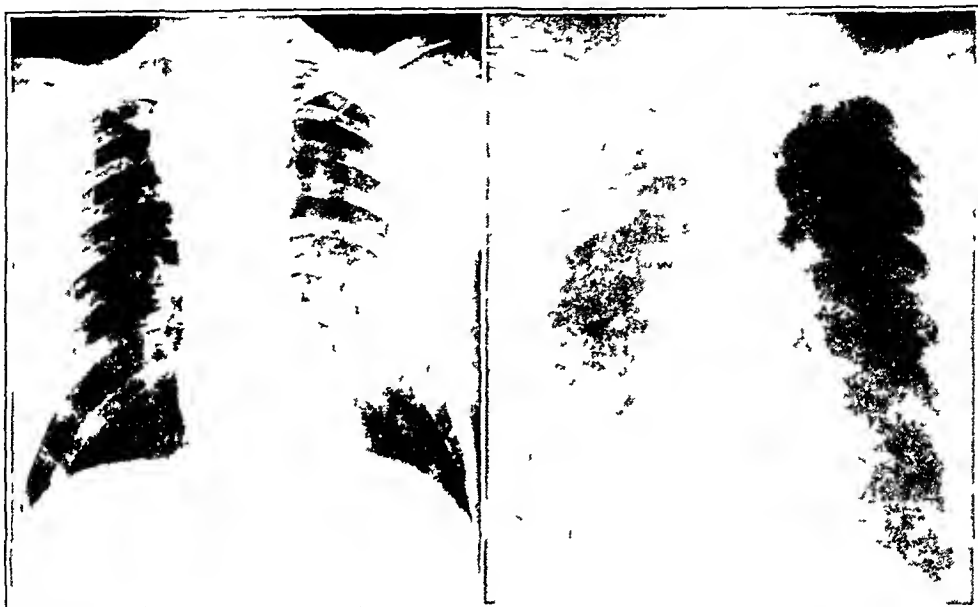
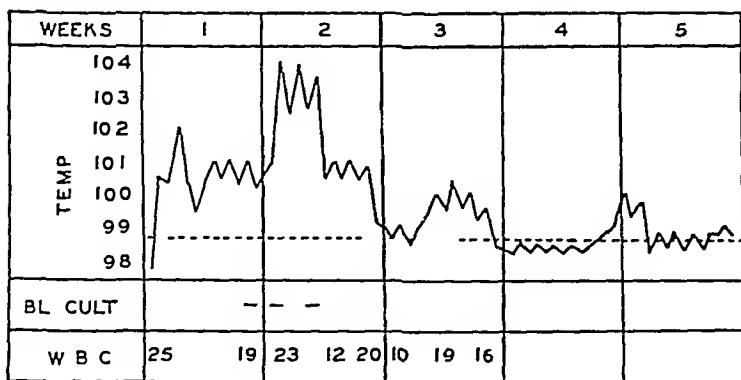


Fig 6 (case 6) —Mediastinitis. The first roentgenogram indicates the condition on the third day of observation, four days before operation. The abscess is seen in the supracardiac area. The aorta is not displaced downward. The shadow is in the posterior mediastinum and projects more to the right than to the left. The second roentgenogram was taken six weeks after the operation. The mediastinum is clear. The defect in the ribs following operation is visible.



↑
OPERATION

Fig 7 (case 6) —Chart showing the temperature curve. The white blood cell counts are recorded in thousands per cubic millimeter.

Fluoroscopic examination showed that this shadow was retroesophageal and in the posterior mediastinum. The esophagus was displaced ventrally and slightly to the left. As the barium entered the esophagus it paused momentarily at this area before passing downward.

Course of the Illness—A chart of the temperature is shown in figure 7. On the seventh day of hospitalization the patient was operated on by Dr. Irving J. Walker. The posterior mediastinum was opened, a portion of the second, third and fourth ribs was resected close to their articulation with the spine, an abscess containing 300 cc. of thin purulent material was opened and a drain was inserted. The pleura was not entered.

After the operation there was an increase in the temperature for several days, but it gradually subsided and returned to normal within twenty-one days. The pus from the abscess showed a pure culture of streptococci, and the drainage was profuse for several weeks. Because of anemia he was given two blood transfusions, and he improved considerably. After several months the cavity gradually diminished so that little drainage was evident. He gained weight and felt greatly improved. When he was seen two months after the operation, he appeared well and had returned to work. There was only a small draining sinus in the back.

In the present case it seems likely that the infection of the posterior mediastinum resulted from an extension of the infective process in the pharynx to the retrovisceral space. The other possibility, of course, is that the abscess arose from suppurating lymph nodes in the posterior mediastinum. This type of infection has been studied extensively by Lerche,¹ who has emphasized the importance of infections of the mediastinal lymph nodes in the causation of mediastinitis. They are analogous to infections of the retropharyngeal lymph nodes with abscess formation in children, the main difference being in the location of the infection.

MEDIASTINAL ABSCESS FOLLOWING INFECTION OF THE RESPIRATORY TRACT

CASE 7—A man aged 25 years complained of pain in the chest and difficulty in swallowing. He had been well until two weeks before admission to the hospital, when he had an illness that was characterized by malaise, generalized aches and pains, and fever. These symptoms soon disappeared, and he felt improved for several days. Then substernal pain on swallowing developed. This pain grew worse, and fever was present. Gradually the pain became more diffuse and could be felt in the region of the ensiform process of the sternum. He then began to have severe pain in the front of the chest that radiated to the back between the shoulder blades. The severe pain lasted five days, and during this time he had a feeling of heaviness and difficulty in swallowing. He could not eat solid food, and he stated that he felt as though there were a mass in the upper part of the chest.

Physical Examination—When he was seen, ten days after the onset of his illness, he complained of fever, pain in the chest and dysphagia. The temperature was 102 F., and he appeared acutely ill. Physical examination showed increased redness of the pharynx and increased dullness to percussion over the spine posteriorly, otherwise it revealed essentially no abnormality.

Laboratory Examination—The white blood cell count was 25,000 per cubic millimeter. A roentgenogram of the chest showed an increase in the width of the shadow in the superior mediastinum, but the lungs were clear.

Course of the Illness—The temperature is charted in figure 8. For the first three days of hospitalization the patient felt somewhat improved, in that the substernal pain was less severe, but the difficulty in swallowing persisted. On the third day there was dulness over the upper lobe of the right lung posteriorly, and numerous rales were heard. On the sixth day he had an attack of coughing and raised half a cupful of blood-streaked material which showed pure culture of hemolytic streptococci. The difficulty in swallowing was slightly relieved, but regurgitation of food and fluid occurred occasionally. A roentgenogram of the chest showed density in the upper lobe of the right lung, and numerous rales were heard over this area. Eight days after the attack of coughing the temperature returned to normal, the signs in the chest gradually subsided, the dysphagia became less, the white blood cell count became normal and he left the hospital, after being there twenty-eight days. He felt well except for slight difficulty in swallowing solid foods. This subsided within two weeks, and he has remained well.

The important features of this case were the attack of grip two weeks before the patient's admission to the hospital and the onset of acute symptoms suggesting a mediastinal abscess, such as substernal pain, painful and difficult swallowing and an increase in the supracardiac

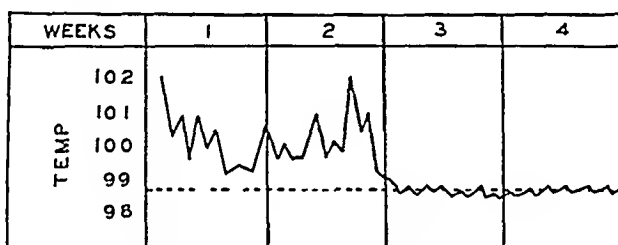


Fig 8 (case 7) —Chart showing the temperature curve for a patient with postinfluenzal mediastinitis. The febrile reaction was of two weeks' duration.

roentgenographic shadow. He finally recovered after the expectoration of the contents of an abscess which had evidently perforated the lung or a bronchus. Hemolytic streptococci were recovered from the expectorated material.

Similar abscesses of the mediastinum following suppuration of lymph nodes have been reported by Lerche,¹ Richards,²⁰ Malnekoff,²¹ Farnum,²² Lambert and Berry,² Fischer,²³ Neuhof,²⁴ and others. These cases are so important as to require special comment. In a few cases the symptoms and signs of mediastinal abscess followed an infection of the respiratory tract which had not been severe or disabling. Lerche¹

²⁰ Richards, L. G. Peritracheal Abscess, *Tr Am Bronch Soc* **12** 71, 1929.

²¹ Malnekoff, B. S. Acute Mediastinal Abscess, *Am J Dis Child* **39** 591 (March) 1930.

²² Farnum, W. B. Acute Suppuration of the Mediastinum, *New York State J Med* **35** 724, 1935.

²³ Fischer, R. C. Abscess of Mediastinum, *J Thoracic Surg* **6** 212, 1936.

²⁴ Neuhof, H. Acute Infection of Mediastinum, *J Thoracic Surg* **6** 184, 1936.

recorded cases in which the abscess appeared, or at least was discovered, three years after an attack of influenza or pneumonia. In several cases recovery followed the expectoration of material contained in the abscess. In one instance the abscess perforated the lung and the esophagus. The history in these cases is of influenza with pneumonia or of influenza followed by cough and frequent colds and after an indeterminate period by pain, dysphagia, cough and dyspnea. Roentgenograms show a shadow in the posterior mediastinum, and there are symptoms and signs of infection. Unless the abscess is drained or aspirated, it often ruptures into the lung, bronchus or esophagus, and in this way recovery may take place, or death may follow from widespread infection. Occasionally empyema arises and obscures the diagnosis, and atelectasis from bronchial pressure has been observed.

It is well to recall, then, that fever and thoracic symptoms following influenza, attacks of pneumonia or sore throat may be due to an abscess in the posterior mediastinum.

CHRONIC ABSCESS OF THE POSTERIOR MEDIASTINUM

A chronic abscess of the posterior mediastinum is almost always due to tuberculosis arising from the vertebrae or from caseous lymph nodes. Other causes for such an abscess are actinomycosis and pyogenic infections of the vertebrae or lymph nodes. This abscess occurs most often in the lower cervical and upper dorsal regions and commonly forms a circumscribed mass that is confused with a solid tumor. It gravitates downward from the point of origin and may appear in the abdominal wall or in the regions where a psoas abscess perforates. Rarely such an abscess perforates a bronchus. Infrequently there is diffuse mediastinitis instead of an abscess and I have observed tuberculous pleuritis after extension of an infection from the spine to the pleura.

The symptoms are due to the primary lesion and to the presence of the space-occupying process in the mediastinum. Fever, pain in the back, dysphagia, cough and gradual wasting are common complaints. The physical signs depend on the size of the abscess and its origin. There is tenderness over the spine in many cases when the vertebrae are the source of the abscess, but in some cases the focus of necrosis in the spine is so small that this sign will be missing. There may be dulness over the upper part of the spine and increase of the whispered voice, indicating a lesion in the posterior mediastinum.

The most important signs are those revealed roentgenographically. This examination should include an anteroposterior and a lateral view of the mediastinum and spine. The shadow cast by the abscess may be in the superior mediastinum or superimposed on the cardiac shadow. There may or may not be demonstrable erosion of the vertebrae.

The shadow is homogeneous, with a sharp convex border. It is almost invariably symmetric and bilateral. It is situated in front of the spine and behind the esophagus, and its axis is parallel with the long axis of the body. It is seen best in the middle or lower part of the posterior mediastinum, it is superimposed on the cardiac shadow and it pushes the esophagus forward.

In general, then, a diagnosis of tuberculous abscess may be made in the presence of low grade fever, pain due to pressure on a nerve and destruction of bone, symptoms of compression of organs, such as the esophagus or bronchi, and roentgenographic changes.

The following two cases illustrate the course of events in tuberculosis of the posterior mediastinum.

CASE 8—A 20 year old girl was first seen in January 1931, complaining of excessive fatigue, dyspnea and slight edema of the ankles of several years' duration. She stated that she had rheumatic fever a number of years previously and that two months before her admission to the hospital a mass of tender red nodules developed over the legs and lasted five weeks. These finally disappeared, and the only abnormality that was found on physical examination at the time of entry was slight enlargement of the heart, with a systolic murmur. There was no fever. The white blood cell count was 6,800 and the hemoglobin value 95 per cent. A roentgenogram of the chest showed a dense area on the right side of the superior mediastinum which did not pulsate when examined by fluoroscopy. An electrocardiogram was normal. The diagnosis at that time was rheumatic heart disease with mitral regurgitation and a mediastinal tumor of unknown etiology. She was discharged from the hospital and followed for several weeks before being readmitted for further examination. For three weeks after her first discharge from the hospital she felt reasonably well, then she began to have fever, chilly sensations, and pain and swelling of the wrists, hands and joints, which seemed to occur after a sore throat. When she reentered the hospital she had a fever and leukocytosis (15,600 leukocytes). A roentgenogram of the chest showed evidence of a mass to the right of the sternum in the superior mediastinum. The heart was moderately enlarged. Electrocardiographic examination showed preponderance of the left ventricle. On more careful questioning it was found that after a sore throat her hands and wrists began to swell and were painful and tender to touch. The entire left arm was likewise painful. There was some stiffness of the left shoulder. After about three days of pain and discomfort the articular symptoms subsided. Four days before entry she had a cough and some soreness in the right side of the chest. There was no sputum. She felt prostrated and chilly and had interrupted sleep. She would awake during the night and drink large quantities of water.

It was thought that the patient had subacute rheumatic fever which followed erythema nodosum and that the cardiac lesion was due to mitral regurgitation. The question of subacute bacterial endocarditis was raised. Culture of the blood made on the day of her admission to the hospital was sterile.

Course of the Illness—For eleven months, while she was observed, there was an irregular fever, the temperature varying daily from 99 to 101 or 102 F and sometimes to 104 F. There was a corresponding elevation of the pulse rate, it varied between 100 and 120 beats per minute. The respiratory rate was normal. Repeated roentgenograms of the chest showed a mass in the superior mediastinum.

It did not pulsate and was considered for some time to be due to Hodgkin's disease. For that reason she was subjected on several occasions to high voltage roentgen therapy over the chest. As the disease progressed, this shadow seemed to diminish somewhat in size, but later it seemed to increase in the lower half of the chest near the mediastinum. On one occasion the patient complained of pain on the right side of the manubrium, there was excruciating tenderness over this area. There was no swelling or pulsation. Nine of the ten blood cultures taken at different intervals during the course of the disease were sterile, one showed a few green streptococci. This finding was never confirmed.

One month after the patient was admitted to the hospital she began to complain of small tender lumps on the back of the chest. These nodules appeared over the tibia, hands and the back. They were well circumscribed, painful and tender to touch. A diagnosis of erythema nodosum was made. These nodules kept recurring from time to time for five months. Some of them broke down and were seen to contain a thick purulent material which was sterile on culture.

Four months before death, signs developed which were interpreted as due to pneumonia of the base of the right lung. There was no cough or expectoration at the time, and after a week or ten days these signs gradually diminished. There was no essential change in the condition until three weeks before death, when she began to notice an increase in the swelling and tenderness of the knee joints. This continued, and the left ankle became swollen. She failed gradually and died eleven months after admission to the hospital.

Laboratory Examination—Electrocardiographic examination showed sinoauricular tachycardia, a PR interval of 0.12 second, a QRS complex of 0.06 second, an upright T wave in leads I and II, an inverted T wave in lead III, preponderance of the left ventricle, but no other changes or abnormalities. The white blood cell count varied from 6,000 to 16,200, the average count being between 5,000 and 8,000 per cubic millimeter. The polymorphonuclear count varied between 80 and 90 per cent and the lymphocyte count between 8 and 16 per cent, the monocyte count was 2 per cent. No abnormal cells were found. The red blood cell count, which was normal on entering, gradually declined to 3,960,000, when the hemoglobin value was 58 per cent. Anemia, however, was not an outstanding feature of her illness. Agglutination tests for undulant fever gave negative results.

Necropsy—Necropsy revealed a mediastinal abscess which had extended into the right pleural cavity and had invaded the eleventh rib, causing interlobar pleurisy. In addition, there was synovitis of both knee joints and the left ankle joint. Microscopic examination showed all these lesions to be due to tuberculosis.

CASE 9—A 20 year old woman was seen for the first time in January 1932, when she complained of pain in the chest, a tired feeling and loss of weight and of appetite of six months' duration. She had previously always been well and healthy. At the age of 17 she married and had two healthy children. The second child was born fourteen months before the patient was seen. There was nothing abnormal about the pregnancy or delivery. She felt well until six months before entry, when she began to notice excessive fatigability and progressive loss of weight and appetite. She consulted her physician, who studied her by means of fluoroscopy and roentgenograms, but nothing definite was found to account for her symptoms.

Four months after the onset of her illness a productive cough developed. The sputum was yellowish and was said to amount to about half a pint daily. On one occasion she raised a small amount of blood-streaked sputum, but after several

weeks the cough and sputum subsided completely. For five weeks before admission to the hospital she remained in bed. During this time she felt hot and had night sweats and insomnia. Her temperature in the afternoon fluctuated between 99 and 101.4 F. She complained of some pain in the thorax and arms, especially the shoulders and elbow joints. Her neck had been stiff for about a month.

Physical Examination—The patient had obviously lost a considerable amount of weight. Her complexion was fair and her skin pale. There was no cyanosis. A careful examination failed to reveal anything abnormal except slight stiffness of the neck in flexion and extension and moderate enlargement of the thyroid gland. There were no physical signs of abnormality of the lungs or heart. The temperature was 100.6 F, the pulse rate 100 and the respiratory rate 20 per minute.

Laboratory Examination—The urine was normal. A blood count showed red blood cells, 4,380,000 per cubic millimeter, hemoglobin, 67 per cent, and white blood cells, 10,000 per cubic millimeter, with 56 per cent polymorphonuclears, 37

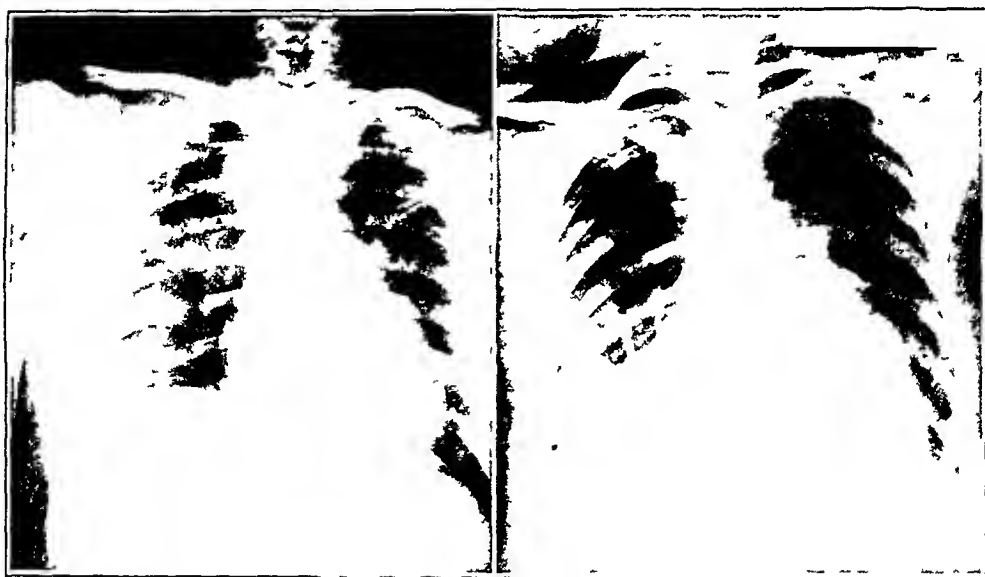


Fig 9 (case 8) —Posterior mediastinitis due to tuberculosis. The first roentgenogram shows a shadow in the upper mediastinum during the third week of observation, the second indicates the mediastinal and pulmonary lesions during the forty-fourth week of illness.

per cent lymphocytes, 3 per cent monocytes, 15 per cent eosinophils and 15 per cent basophils. The stained smear appeared normal. The sedimentation rate was increased over normal. Culture of the blood was sterile, and the stool was normal. The basal metabolic rate was plus 3 per cent. The reaction to the tuberculin test (1:100) was positive. The nonprotein nitrogen content of the blood was 19 mg per hundred cubic centimeter. Numerous roentgenograms of the chest, mediastinum and cervical portion of the spine were made. The lungs were within normal limits. The cervical portion of the spine showed a thickening of the musculature anterior to the spine, with displacement of the trachea forward. A thick barium meal showed that the esophagus was displaced forward and slightly to the left by a symmetric mass which cast a triangular shadow in the lower cervical and upper thoracic portions of the spine. The cervical portion of the spine appeared normal.

Course of the Illness—The patient was under observation for three months. For the first five weeks of observation her temperature ranged daily from 99 to 100.5 or 101 F. When she left the hospital her temperature ranged between normal and 99.6 F in the afternoon. Her weight increased from 89 to 112 pounds (51 Kg) during the three months.

Numerous examinations of the blood failed to show any alteration in the white blood cells. The total count varied between 7,500 and 10,000 per cubic millimeter. The hemoglobin value increased while the patient was under observation from 67 to 85 per cent, and the red blood cell count increased from 4,380,000 to 5,380,000 per cubic millimeter. It was not possible to obtain any sputum for examination, and tuberculosis was never proved as far as infection of the lung was concerned. She left the hospital, returned to her home and was not seen for three years.

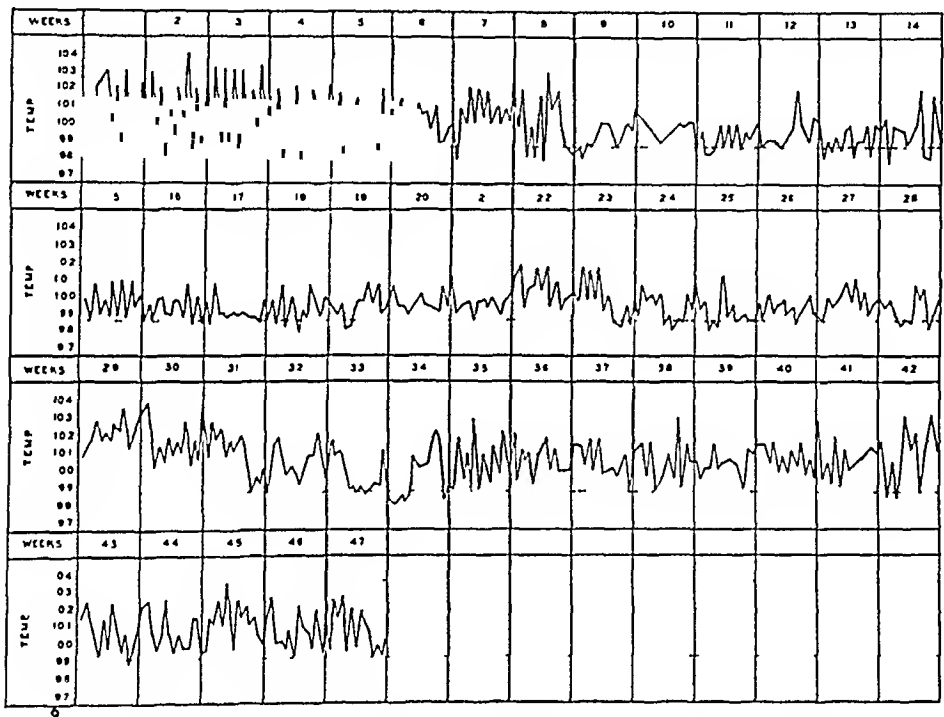


Fig 10 (case 8)—Chart showing the temperature curve

After her discharge from the hospital, in 1932, she remained well, gained weight and had no complaints until the autumn of 1934, when she began to notice malaise, fatigability and fever, with anorexia and progressive loss of weight. After these symptoms continued for several months a new symptom appeared—dysphagia, with a choking sensation in the throat which provoked an unproductive cough. These symptoms continued unabated until she returned to the hospital in February 1935, when she complained of recurrent headaches and severe pain in the neck and spine of several months' duration.

The examination in 1935 showed that the patient was uncomfortable. The face was flushed, and she had obviously lost a considerable amount of weight. The temperature was elevated above normal, the pulse and respiratory rates were increased. Examination revealed tenderness over the seventh cervical and the first dorsal vertebra. The lungs were clear, and the heart, abdomen and extremities were normal. The blood showed evidence of hypochromic anemia. The sedi-

mentation rate was increased, the reaction to the tuberculin test was positive and agglutination tests for *Bacillus typhosus*, *Bacillus paratyphosus* and *Bacillus melitensis* gave a negative reaction. Roentgenograms of the chest are shown in figure 12. The conspicuous feature was the bilateral shadow in the posterior and in the superior mediastinum, with a sharp, well defined border, broader in its cephalic portion. Anterior and lateral views of the cervical portion of the spine were normal. An incidental finding was bilateral cervical rib. The mass was retrotracheal and had displaced the trachea anteriorly, the esophagus was displaced anteriorly and to the left of the midline.

The record of the temperature is shown in figure 11. It is noticeable that there was irregular fever for eighteen weeks. During this time the patient lost weight and strength. The physical findings so far as the chest was concerned did not change. Gradually the temperature became lower. She entered a sanatorium for tuberculous patients for further treatment and remained for six months. During this time she improved continually, gaining weight and strength,

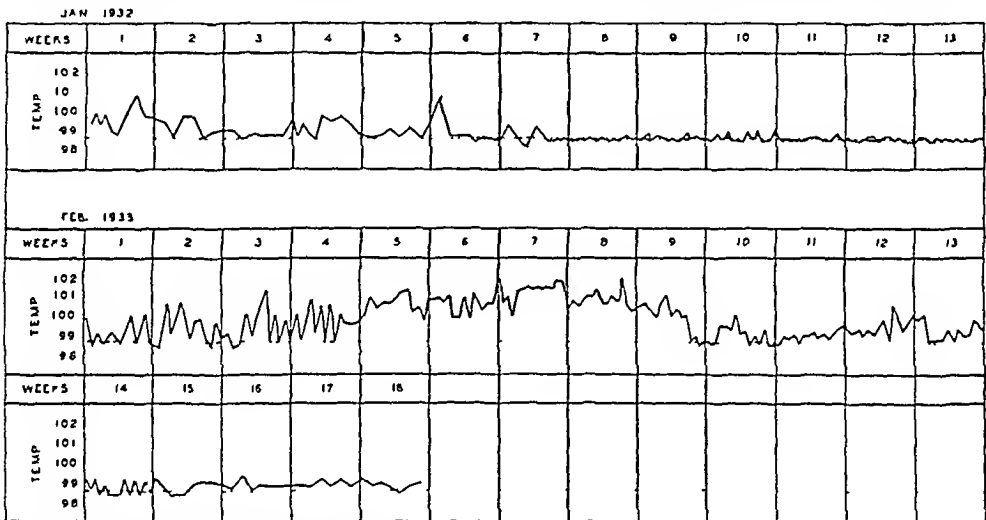


Fig 11 (case 9) —Chart showing the temperature curves for a patient with mediastinitis due to tuberculosis during two periods of hospitalization

her temperature remained normal and she returned home after rest and general upbuilding.

After leaving the sanatorium she remained well and when seen in 1937 had no complaints. Roentgenograms failed to show any change in the spine, and the shadow in the mediastinum which had been present in 1932 and 1935 had disappeared completely.

Summary—A young woman, who was followed for over five years, had two prolonged bouts of fever without leukocytosis but with signs of an abscess in the mediastinum which was probably tuberculous in origin. This was present in spite of the fact that no signs of Pott's disease could ever be elicited. Recovery followed conservative treatment.

While the precise etiologic diagnosis was not made in this case, the repeated attacks of fever, the chronicity and the location of the infective process and the strongly positive reaction to the tuberculin test were all in favor of tuberculosis. This case serves to illustrate that a tuberculous abscess may be located in the posterior mediastinum with-

out a roentgenographically demonstrable lesion in the spine. Failure to demonstrate such a lesion roentgenographically does not exclude this focus. Heuer has recorded a case in which an abscess of the posterior

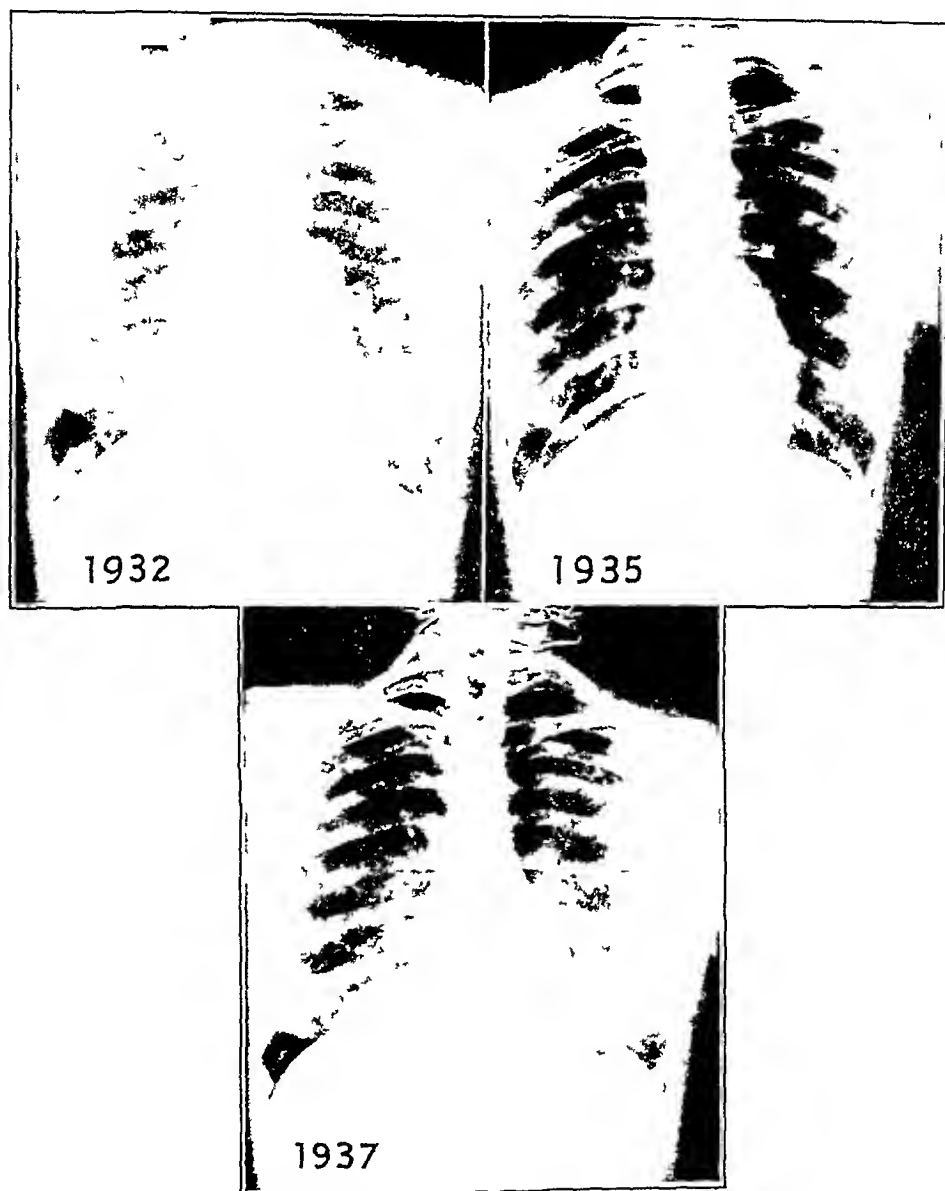


Fig 12 (case 9) —The roentgenograms taken in 1932 and 1935 show an abscess in the posterior mediastinum. By 1937 it had disappeared.

mediastinum followed caries of the spine, it was not possible to demonstrate the area of necrosis in the vertebrae roentgenographically, but it was present at the time of operation. It is also impressive that such an abscess can resolve spontaneously with conservative treatment.

MEDIASTINITIS FOLLOWING PNEUMONIA

During the pandemic of influenza in 1918 numerous cases of mediastinitis due to hemolytic streptococci²⁵ were reported, and it was repeatedly pointed out that the mediastinal lymph nodes in fatal cases were swollen and suppurating. This diffuse infection of the mediastinum was always a serious complication, as the following case illustrates.

CASE 10—A young man was admitted to the hospital with lobar pneumonia due to type I pneumococci with bacteremia. In spite of the administration of large amounts of antipneumococcus horse serum, his temperature did not return to normal. It was then found that he had a mixed infection, since the sputum contained large numbers of hemolytic streptococci as well as pneumococci. On the eleventh day of his illness there were signs of mediastinopericarditis, with a loud friction rub which was synchronous with the heart beat and which was exaggerated by respiration. On the thirteenth day hoarseness developed, and he

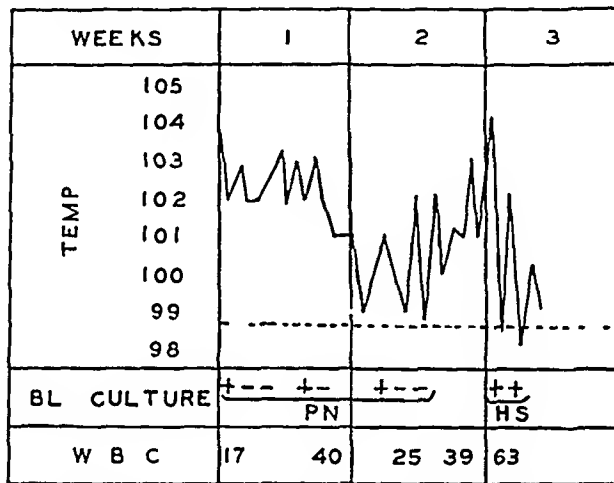


Fig 13 (case 10)—Chart showing the temperature curve in a case of mediastinitis following pneumonia. The first three cultures of the blood showed type 1 pneumococci, the last two, hemolytic streptococci. The white blood cell count is recorded in thousands per cubic millimeter.

was unable to speak above a whisper, the following day he had pain under the gladiolus and difficulty in swallowing. He died on the seventeenth day of his illness. The results of culture of the blood, the white blood cell counts and the temperature chart are shown in figure 13.

The necropsy showed resolving pneumonia on the right side, with many abscesses of the lung, diffuse mediastinitis and empyema (hemolytic streptococci) on the right side in the anterior mediastinal pleural space.

This case emphasizes two points: first the seriousness of mediastinitis in lobar pneumonia and, second, the importance of mixed infections in this disease, a feature that has been studied and reviewed most thoroughly by Finland,²⁶ Parsons and Myers²⁷ and Solomon and

²⁵ Farnum ²² Fischer ²³

²⁶ Finland, M. The Significance of Mixed Infections in Pneumococcic Pneumonia, J A M A **103** 1681 (Dec 1) 1934.

²⁷ Parsons, J W, and Myers, W K. Streptococcic Sepsis Complicating Recovery from Pneumococcic Pneumonia, J A M A **100** 1857 (June 10) 1933.

Curphey²⁸ It also emphasizes the importance of substernal pain and dysphagia in the diagnosis of mediastinitis

COMMENT

The cases reported in this paper illustrate that an acute abscess or a chronic inflammatory lesion of the mediastinum may occur as a result of a variety of infections. In some cases the process is only part of a more widespread and extensive process, and for that reason it is of interest only so far as the complete diagnosis is concerned. In other cases, however, an abscess is the principal lesion, and when recognized it can be treated with a reasonable degree of success. For this reason it is necessary to recognize the conditions which cause mediastinal abscess and to be familiar with the features in these cases.

SUMMARY AND CONCLUSIONS

From a study of sixty cases of acute and of chronic mediastinitis the following conclusions are justified.

Acute and chronic mediastinal infections are most common in the posterior mediastinum.

The common causes of posterior mediastinitis are perforation of the esophagus and suppurative lymph nodes. Other causes are lesions in the spine, lungs, pleura and abdomen. Infections due to tubercle bacilli or hemolytic streptococci are frequent causes.

Abscess of the anterior mediastinum results most often from an infection in the neck or from osteomyelitis of the sternum. A chronic infection in this location is usually due to tuberculosis or syphilis.

The diagnosis of mediastinal abscess depends on (1) the presence of a condition which is capable of producing mediastinal infection, (2) the symptoms and signs of an infection, with local physical signs referable to the mediastinum, and (3) the results of aspiration or exploration.

On the whole, the prognosis in mediastinal abscess is poor, largely because of the presence of the process that is responsible for the abscess. When the process is localized to a part of the mediastinum which is accessible for surgical treatment, the prognosis is better.

Chronic fibrous mediastinitis is due to healed or active tuberculosis, syphilis or pyogenic infection. There is often an associated fibrous pericarditis, so that the clinical picture may be that of congestive heart failure due to cardiac compression.

Cardiac failure with congestion may also accompany mediastinitis when there is an associated defect of the mitral valve or an aneurysm of the aorta compressing the pulmonary artery. When this is the case the mediastinitis may be latent or may play only a small part in the clinical features.

²⁸ Solomon, S., and Curphey, T. J. Streptococcic Septicemia Complicating Pneumococcic Lobar Pneumonia, *J. A. M. A.* **108** 187 (Jan 16) 1937.

INFLUENCE OF DIARRHEA ON THE VITAMIN B₁ REQUIREMENT

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AND

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Chronic diarrhea occurs as a symptom in a great variety of diseases (table 1) In the management of the majority of these conditions, one of the problems of prime importance is the assurance of an adequate supply of dietary essentials Without intending to minimize the importance of mineral constituents or of the other substances known to be necessary in the diet, we present this study concerned with one particular aspect of the problem, namely, the amount of vitamin B₁ which may be required by patients suffering from diarrhea

The literature contains abundant clinical evidence that disorders due to dietary deficiencies, usually multiple but particularly of the vitamins of the B complex, occur as complications of chronic diseases of the alimentary tract Signs and symptoms of pellagra and beriberi have been observed in carcinoma of the gastrointestinal tract (Rolph,¹ 1916, Eusterman and O'Leary,² 1931), in ulcerative colitis (Barnes,³ 1926, Mackie,⁴ 1935) and after short-circuiting operations on the intestines

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Throughout this paper the term milligram equivalent is used to indicate 0.05 U S P unit (Cowgill, G R The Vitamin B Requirement of Man, New Haven, Conn, Yale University Press, 1934)

* Fellow of the Henry Strong Denison Foundation for Medical Research, 1934-1935 The data presented in this article are from a thesis submitted to the faculty of the Yale University School of Medicine in partial fulfilment of the requirements for the degree of Doctor of Medicine

1 Rolph, F W Cancer of the Stomach and Pellagra in the Same Patient, *Canad M A J* **6** 323-324 (April) 1916

2 Eusterman, G B, and O'Leary, P A Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastrointestinal Tract, *Arch Int Med* **47** 633-649 (April) 1931

3 Barnes, J M Typical Pellagra Syndrome Developing in Patient with Chronic Ulcerative Colitis While Under Hospital Treatment, *Ann Clin Med* **4** 552-564 (Jan) 1926

4 Mackie, T T Ulcerative Colitis II The Factor of Deficiency States, *J A M A* **104** 175-178 (Jan 19) 1935

(Jones,⁵ 1933, Urmey, Ragle, Allen and Jones,⁶ 1934) In the treatment of patients with chronic diarrheal conditions, particularly ulcerative colitis, Larimore⁷ (1928), Bargaen and Victor⁸ (1931) and others have advocated the administration of diets rich in vitamins, especially vitamin B. Bargaen and Victor have recommended the addition of 200 mg of brewers' yeast daily to the bland diet usually tolerated by these patients.

In the treatment of bacillary dysentery the value of "vitamin preparations given with a definite purpose in view and not haphazard" has been mentioned by Corner⁹ (1935), and the specific value of parenteral administration of vitamin B₁ in a form of infantile diarrhea prevalent in Palestine has been described by Grunfelder and his colleagues¹⁰

TABLE 1—*Classification of Etiologic Factors in Chronic Diarrheas**

I Infectious and parasitic diseases	VI Allergic disorders
Bacillary dysenteries	VII Chronic passive congestion
Amebic dysentery	Cardiac failure
Tuberculosis of the gastrointestinal tract	Cirrhosis of liver
Diseases due to other organisms	VIII Operative procedures
II Toxic disorders	Intestinal resection
Polsoning due to mercury, arsenic, etc	Malfunctioning gastroenterostomy
Uremia	IX Gastrogenic disorders
III Endocrine disorders	Achylia
Addison's disease	Delayed emptying
Thyrotoxicosis	X Irritative disorders
IV Neoplasms	Fermentative and putrefactive conditions
V Deficiency states	XI Neurogenic and psychogenic disorders
Beriberi	XII Disorders of unknown etiology
Sprue	Ulcerative colitis
Pellagra	Regional ileitis

* Modified from classifications published by H. W. Bettman (Diarrhea, in Nelson Loose Leaf Living Medicine, New York: Thomas Nelson & Sons, 1934, vol. 5, pp. 355-364), J. L. Kantor (Treatment of Common Disorders of Digestion, ed. 2, St. Louis, C. V. Mosby Company, 1929, p. 242, Diarrhea, Am. J. Digest. Dis. & Nutrition 2: 17 [March] 1935) and F. W. Brown (Diagnosis and Treatment of Certain Types of Chronic Diarrhea, Ann. Int. Med. 8: 93-99 [July] 1934).

5 Jones, C. M. Peripheral Complications of Ulcerative Colitis, M. Clin. North America 16: 919-928 (Jan.) 1933

6 Urmey, T. V., Ragle, B. H., Allen, A. W., and Jones, C. M. Beriberi Secondary to Short-Circuited Small Intestine, New England J. Med. 210: 251-254 (Feb. 1) 1934

7 Larimore, J. W. Chronic Ulcerative Colitis. Observations of Treatment by Diet, Tr. Am. Gastro-Enterol. A. 30: 298-318, 1928

8 Bargaen, J. A., and Victor, M. Diet in Intestinal Disorders, J. A. M. A. 97: 151-154 (July 18) 1931

9 Corner, H. W. Bacillary Dysentery. A Summary of Treatment, Brit. M. J. 1: 1162-1165 (June 8) 1935

10 Grunfelder, B., Rabinovici, E., Geiger, A., and Rosenberg, A. Ueber die therapeutische Wirkung von intravenos verabreichtem B Vitamin in der Behandlung der Ernährungsstörungen mit toxischen Erschütterungen bei Säuglingen, Klin. Wchnschr. 12: 983-985 (June 24) 1933

(1933) The controversy as to whether vitamin therapy is of any avail in intestinal tuberculosis, illustrated by the reports of McConkey¹¹ (1930) and of Steinbach and Rosenblatt¹² (1935) pro and con, respectively, may be due in part to the fact that in the administration of vitamins physicians have had little information as to how much of each vitamin is actually needed by the patient

Few data have been available on which to base quantitative prescriptions. In the present investigation an approach to the problem has been made by determinations of the effect of diarrhea on the vitamin B₁ requirement of dogs under various conditions. The clinical value of such experiments depends, first, on the accuracy of the methods used and, second, on the applicability of the results to human beings. An accurate determination of the individual animal's requirement for vitamin B₁ under any desired conditions has been made possible and relatively easy by a standardized method that has been devised (Cowgill, Deuel and Smith,¹³ 1925) to utilize the appearance of the specific anorexia which develops as an early sign of deficiency of this dietary essential. After the development of this method and the determination of the normal requirement of the dog, we undertook an extensive research project to discover the influence on the vitamin B₁ requirement under a number of conditions, including exercise (Cowgill, Rosenberg and Rogoff¹⁴ 1931), disease of the thyroid gland (Himwich, Goldfarb and Cowgill,¹⁵ 1932), fever (Cowgill and Dann,¹⁶ 1936) and diuresis (Cowgill, Rosenberg and Rogoff,¹⁷ 1930). The present study is a part of this series of experiments

11 McConkey, M. The Treatment of Intestinal Tuberculosis with Cod Liver Oil and Tomato Juice, *Am Rev Tuberc* **21** 627-635 (May) 1930

12 Steinbach, M. M., and Rosenblatt, M. B. Vitamin Therapy in Intestinal Tuberculosis, *Am Rev Tuberc* **31** 35-43 (Jan) 1935

13 Cowgill, G. R., Deuel, H. J., Jr., and Smith, A. H. Studies in the Physiology of Vitamins. III Quantitative Aspects of the Relation Between Vitamin B and Appetite in the Dog, *Am J Physiol* **73** 106-126 (June) 1925

14 Cowgill, G. R., Rosenberg, H. A., and Rogoff, J. Studies in the Physiology of Vitamins. XVI The Effect of Exercise on the Time Required for the Development of the Anorexia Characteristic of Lack of Undifferentiated Vitamin B, *Am J Physiol* **98** 589-594 (Nov) 1931

15 Himwich, H. E., Goldfarb, W., and Cowgill, G. R. Studies in the Physiology of Vitamins. XVII The Effect of Thyroid Administration upon the Anorexia Characteristic of Lack of Undifferentiated Vitamin B, *Am J Physiol* **99** 689-695 (Feb) 1932

16 Cowgill, G. R., and Dann, M. The Failure of Dinitrophenol to Influence the Vitamin B Requirement, *Yale J Biol & Med* **8** 501-509 (May) 1936

17 Cowgill, G. R., Rosenberg, H. A., and Rogoff, J. Studies in the Physiology of Vitamins. XIV The Effect of Administration of Large Amounts of Water on the Time Required for Development of the Anorexia Characteristic of a Deficiency of the Vitamin B Complex, *Am J Physiol* **95** 537-541 (Dec) 1930

As far as the normal vitamin B₁ requirement of man is concerned, the applicability of data derived from experiments on dogs and other animals to its estimation has been abundantly proved. On the basis of evidence that the requirement in several species is a function of the body weight and of the metabolic rate of the organism, the formula for man has been evolved (Cowgill,¹⁸ 1934)

$$\frac{\text{Vitamins (mg)}}{\text{Calories}} = 0.0000284 \times \text{Weight (Gm)}$$

In this formula the daily vitamin B₁ requirement is given in milligrams of a standard yeast concentrate (milligram equivalents), and the calories represent the individual's daily total caloric intake. The validity of this formula is established by means of extensive calculations of the vitamin B₁ content of a number of diets for human beings and excellent correlation between their conformity to the formula and their ability to protect against beriberi. Further confirmation of this work may be found in the study of Baker and Wright¹⁹ (1936), and proof of the clinical usefulness of the formula has appeared in independent clinical reports (Jolliffe and Colbert,²⁰ 1936, Goodhart and Jolliffe,²¹ 1938), showing that so-called alcoholic polyneuritis is not improved in patients whose vitamin-calory ratio is low or borderline but that marked improvement is obtained when excess vitamin B₁ is administered. As data derived from experiments on dogs have already proved useful in application to dietary problems of human beings, a study of the effect of diarrhea on the vitamin B₁ requirement of dogs may therefore be considered a valid means of approach to the question of the amount of this vitamin which should be made available to patients suffering from diseases in which chronic diarrhea is a symptom. As a result of the present study, some conclusions will be presented not only as to the quantities desirable but also as to the relative values of various sources and routes of administration of the vitamin.

In addition to the possible clinical application of determinations of the vitamin B₁ requirement of dogs with diarrhea, the data may also shed some light on the question of the mode of excretion of this factor. The fact that this vitamin is excreted in the urine and that the amount bears some relation to the dietary intake has been demonstrated by

18 Cowgill, G. R. *The Vitamin B Requirement of Man*, New Haven, Conn., Yale University Press, 1934.

19 Baker, A. Z., and Wright, M. D. Vitamin B₁ in Human Diets, *Proc. Roy. Soc. Med.* **29** 1145-1154 (July) 1936.

20 Jolliffe, N., and Colbert, C. N. Etiology of Polyneuritis in the Alcohol Addict, *J. A. M. A.* **107** 642-647 (Aug. 29) 1936.

21 Goodhart, R., and Jolliffe, N. Effects of Vitamin B (B₁) Therapy on the Polyneuritis of Alcohol Addicts, *J. A. M. A.* **110** 414-419 (Feb. 5) 1938.

Muckenfuss²² (1918), Van der Walle²³ (1922) and Harris and Leong²⁴ (1936) In this connection, certain of our previous experiments (Cowgill, Rosenberg and Rogoff,¹⁷ 1930) are interesting They showed that diuresis produced by forcing fluids more than doubled the dog's requirement for vitamin B₁, as measured by the time necessary for anorexia to develop after the animal had been given an opportunity to store a maximum amount of the vitamin in the tissues and then was given a diet free from this factor This effect was attributed to a washing out of the vitamin

The direct estimation of the vitamin B₁ content of the feces cannot be used to determine the excretion of this material by the intestinal route, because of its presence in the stools of animals not receiving any vitamin B₁ in the diet, presumably as a result of multiplication of intestinal bacteria whose bodies contain this vitamin (Steenbock, Sell and Nelson,²⁵ 1923, Salmon,²⁶ 1925, Damon,²⁷ 1923 and 1924, Heller, McElroy and Garlock,²⁸ 1925, Sunderlin and Werkman,²⁹ 1928, Cowgill and Weinstein³⁰)

However, indirect evidence as to the importance of the intestines in the loss of vitamin B₁ might be obtained by means of experiments in which diarrhea was produced, analogous in some respects to the diuresis experiments (Cowgill, Rosenberg and Rogoff¹⁷) performed in 1930 From a theoretic standpoint, diarrhea might operate to increase the body's need for vitamin B₁ by bringing about a loss of the vitamin stored in the tissues, through excretion into the intestines along with the fluid which forms so large a part of the diarrheal stool A differentiation

22 Muckenfuss, A M The Presence of Food Accessories in Urine, Bile and Saliva, *J Am Chem Soc* **40** 1606-1611, 1918

23 Van der Walle, N The Presence of the Antineuritic and Antiscorbutic Vitamins in Urine, *Biochem J* **16** 713-726, 1922

24 Harris, L J, and Leong, P C Vitamins in Human Nutrition The Excretion of Vitamin B₁ in Human Urine and Its Dependence on the Dietary Intake, *Lancet* **1** 886-894 (April 18) 1936

25 Steenbock, H, Sell, M T, and Nelson, E M Vitamin B I A Modified Technique in the Use of the Rat for Determinations of Vitamin B, *J Biol Chem* **55** 399-410 (March) 1923

26 Salmon, W D Vitamin B in the Excreta of Rats on a Diet Low in This Factor, *J Biol Chem* **65** 457-462 (Sept) 1925

27 Damon, S R Some Observations in Regard to Growth-Promoting Substances of Bacterial Origin, *J Biol Chem* **56** 895-902 (July) 1923, Acid-Fast Bacteria as a Source of Vitamin B, *J Path & Bact* **27** 163-169 (April) 1924

28 Heller, V G, McElroy, C H, and Garlock, B The Effect of the Bacterial Flora on the Biological Test for Vitamin B, *J Biol Chem* **65** 255-264 (Aug) 1925

29 Sunderlin, G, and Werkman, C H Synthesis of Vitamin B by Microorganisms, *J Bact* **16** 17-33 (July) 1928

30 Cowgill, G R, and Weinstein, L Unpublished data

between the amount of the vitamin which merely escapes absorption and that which may be actively excreted through the intestinal tract can be made by arranging conditions so that in some of the experiments the dogs ingest small amounts of vitamin B₁ daily and so that impairment of absorption plays a major role, whereas in others this factor is excluded either by giving the vitamin parenterally or by inducing diarrhea only after the animals have had an opportunity to store a maximum amount of it in their tissues

The experiments reported here are designed, therefore, with a two-fold purpose, first, to obtain data which may be applicable to an estimation of the vitamin B₁ requirement of patients suffering from diarrheal conditions and, second, to contribute to available knowledge of the mode of excretion of this vitamin

EXPERIMENTAL METHODS

The methods used in this investigation consisted of two principal procedures, both of which were derived from the observations made in 1925 (Cowgill, Deuel and Smith³¹) and were based on the production in dogs of anorexia shown (Cowgill, Rosenberg and Rogoff,³¹ 1931, Burack and Cowgill,³² 1931, Sherman and Sandels,³³ 1931) to be specific for the antineuritic vitamin B (B₁)

A group of 9 young adult mongrel dogs, weighing between 6 and 11 Kg, was employed. Every dog was observed at the beginning to have a normal appetite and was given a vermifuge to assure freedom from intestinal parasites. The diet consisted of an artificial mixture of casein, sucrose, lard, butter, bone ash and certain mineral salts, known to be practically free from vitamin B, which was described (Cowgill³⁴) in 1923 and designated as the casein III diet. The supplements are listed in table 2. At the time these experiments were conducted, pure crystalline vitamin B₁ was not yet available. Since complex mixtures had to be used, widely different sources were chosen, so that if quantitatively comparable results should be obtained, they could be attributed specifically to the vitamin and not to any other components of the materials. These substances were assayed

31 Cowgill, G. R., Rosenberg, H. A., and Rogoff, J. Studies in the Physiology of Vitamins. XV. Some Observations of the Effect of Administration of the Antineuritic and Heat Stable Factors on the Anorexia Characteristic of Lack of the Vitamin B Complex, *Am J Physiol* **96** 372-376 (Feb.) 1931

32 Burack, E., and Cowgill, G. R. Anorexia Characteristic of Lack of the Vitamin B Complex. The Roles of the Individual Components, *Proc Soc Exper Biol & Med* **28** 750-752 (April) 1931

33 Sherman, H. C., and Sandels, M. R. Further Experimental Differentiation of Vitamins B and G, *J Nutrition* **3** 395-409 (Jan.) 1931

34 Cowgill, G. R. Studies in Physiology of Vitamins. II. Parenteral Administration of Vitamin-B—Mammalian Experiments, *Am J Physiol* **66** 164-175 (Sept.) 1923

in this laboratory, the pigeon method (Block, Cowgill and Klotz,³⁵ 1932) being used. The values found corresponded well with those claimed by the manufacturers.

Series 1 consisted of "saturation" experiments, in which the tissues were first given opportunity to store vitamin B₁. Each dog, after receiving a stock diet, was transferred to the casein III diet and at the same time given large portions of substances rich in vitamin B₁. Usually 50 Gm of yeast was administered one day, followed by 50 Gm of wheat germ the next day, or else two 50 Gm portions of either material was given. In some instances 10 Gm of liver extract was also administered, to make doubly sure that vitamin B₂ (or G) was also present in abundance.

The animal was then allowed to subsist on the vitamin B₁ deficient diet, a daily weighed amount being provided which was sufficient for its caloric needs. Invariably a day came, after a period varying for different animals from ten to twenty-four days, when only a part of the ration was consumed, and on the following day part of or all the food was again refused. The number of days during which there was a perfect appetite was taken as the significant figure, but the experiment was not considered complete until checked as follows. The dog was given

TABLE 2—*Sources of Vitamin B₁*

	Vitamin B ₁ Value	
	Milligram Equivalents*	U S P Units
Yeast, dried brewers' †	116 per Gm	5.8 per Gm
Wheat germ ‡	132 per Gm	6.6 per Gm
Rice polishings extract §	1,193 per cc	59.6 per cc

* One milligram equivalent (Cowgill,¹⁸ 1934) equals 0.05 U S P units.

† Supplied by the Northwestern Yeast Co., Chicago.

‡ The wheat germ used was embo, a product of General Mills, Inc., Minneapolis, supplied for experimental purposes by Dr. C. H. Bailey, director of research.

§ An extract suitable for subcutaneous injection was made by Eli Lilly Co. according to the method previously described (Stuart, Block and Cowgill,³⁷ 1934). The concentrate was furnished for this research project by D. H. W. Rhodchamel, director of research.

a small dose of beef extract³⁶ which was free from vitamin B₁ and one or two days later a small dose of a potent source of the vitamin. In every case the appetite for the usual daily amount of the casein III diet was restored by the latter for at least one day but never by the former.

The dog was then brought as nearly as possible to the same nutritional condition as before the experiment was begun by being given the stock diet, usually for at least three weeks before the next experiment was started. In this experiment the effect of diarrhea was determined. A procedure identical with that previously described was used, except that beginning on the day after the second large dose of vitamin B₁ was given, magnesium sulfate was administered daily. This saline cathartic was chosen in order to produce mild diarrhea, compatible with maintenance of normal weight and health. This drug acts on both the small and the large intestine by osmosis, causing retention and excretion of water in the alimentary tract, with little of the irritative and toxic actions characterizing

35 Block, R. J., Cowgill, G. R., and Klotz, B. H. The Antineuritic Vitamin I. The Method of Assay, Concentration of the Vitamin with Silver Under Various Conditions, and Its Solubility in Certain Organic Solvents, *J. Biol. Chem.* **94** 765-782 (Jan.) 1932.

36 Liebig's extract of beef, Lemco, was used.

other types of purgatives. Dogs receiving enough magnesium sulfate daily to cause loose or fluid stools for weeks at a time appeared as healthy and lively as when they were not receiving the drug and did not lose weight. Usually from 3 to 5 Gm was found sufficient. The drug was given in gelatin capsules at the same time that the food was put into the cage. Considerable individual variation was seen in the time of day at which the soft or fluid stools appeared, the average time being about eight hours after the administration of the laxative.

In series 2 and 3, which differed only as to the form in which the vitamin was administered, the guiding principle of the experiment was that of preventing anorexia by the smallest possible daily dose of vitamin B₁ while the animal was receiving the deficient diet.

In the experiments in series 2 each dog was allowed to subsist on the ration that was free from vitamin B₁ until anorexia developed. The next day a supplement containing vitamin B₁ was given, usually 0.3 Gm of yeast or wheat germ per kilogram. If the animal refused to eat all its daily portion of the casein III diet, the dose of the vitamin preparation was increased, usually by about 0.2 Gm. Similar increments were added each day until a dose was reached which caused the appetite to be restored. This apparently adequate dose was continued for ten days.

In other dogs the trial dose was found sufficient to maintain the appetite. In these cases the initial dose was continued daily for ten days, after which it was decreased, usually by about 10 per cent. This procedure was repeated until a dose was reached at which the dog refused to eat all its ration for two or more days. The previous dose, with which it had eaten well for ten days, was then administered, and usually the appetite was restored. A difference of 0.2 Gm per day in the total dose of the yeast or wheat germ given by mouth usually made the difference between refusal of at least part of the diet free from vitamin B₁ and willingness to eat the entire portion. In some cases when the animals did not immediately consume all the vitamin supplement from a dish, the vitamin was given in gelatin capsules.

The requirement for each dog was determined by the method outlined in two periods, one in which there was no diarrhea and the other in which the dog received sufficient magnesium sulfate to produce liquid stools daily. In some instances the period of diarrhea preceded the one without diarrhea, and in some it followed this period. In some cases the required dosage was reached by increasing doses and in some by decreasing ones.

This method possesses the advantages that the daily requirement can be stated in units of vitamin B₁ and that a comparison can be made between different substances and also between various routes of administration. The justification for using a period as short as ten days in establishing the criterion of the minimal daily dose is that in a number of preliminary experiments not included in this paper it was found that the results for any dog could be obtained again with fairly reasonable agreement (table 5, dog 2). Also, the average daily requirement of orally administered vitamin B₁ found under normal conditions by this method (355 milligram equivalents per kilogram of body weight) corresponds closely with the value (40 milligram equivalents per kilogram per day) obtained (Cowgill, Deuel and Smith,¹³ 1925) for dogs which were maintained on the minimal daily dose necessary to preserve appetite for two months or more.

The procedure in series 3 was identical with that in series 2, except that instead of an oral dose of vitamin B₁, a source of this vitamin was administered subcutaneously in the form of a rice polishings concentrate. The preparation as

obtained from the manufacturer (Stuart, Block and Cowgill,³⁷ 1934) was diluted ten times with sterile physiologic solution of sodium chloride and administered with aseptic precautions. As a trial dose for starting, 0.02 cc per kilogram was the usual amount, and after the end point had been reached, a difference of 0.02 cc in the total dose was usually significant.

It is apparent that either parenteral administration or the method used in series 1, in which the animals were given sufficient vitamin B₁ before diarrhea started to saturate their tissues, would obviate the loss of vitamin by failure of intestinal absorption. On the other hand, in series 2, in which the vitamin was given in daily oral doses, it might be expected that lack of absorption during diarrhea would play a major role. By these varied procedures any excretion of vitamin B₁ through the intestinal tract, which might be enhanced by the diarrhea, could be distinguished from simple failure of absorption.

TABLE 3—*Effect of Diarrhea on Vitamin B₁ Requirement of Dogs After "Saturation" Doses (Series 1)*

Dog	Without Diarrhea		With Diarrhea		Difference Between <i>a</i> and <i>b</i> , Days
	Body Weight, Kg	Period of Perfect Food Intake (<i>a</i>), Days	Body Weight, Kg	Period of Perfect Food Intake (<i>b</i>), Days	
1	11.2	12	11.1	15	+3
2	9.2	13	8.9	12	-1
3 (<i>a</i>)	8.0	14			
(<i>b</i>)	7.3	10			
		Average			
4	7.5	12	10.3	12	0
5	9.9	11	8.7	12	+1
6	9.9	24	10.7	18	-6
	6.2	22	7.5	17	-5

RESULTS

The results of series 1 (table 3) indicate that diarrhea following adequate storage of vitamin B₁ has little effect on the time required for depletion to the level of anorexia. For 4 of the 6 dogs studied by this method the differences in length of the period of perfect appetite with and without diarrhea were no, one, one and three days, respectively, which are within the limit of error of the method, as illustrated by the difference of four days found in 2 experiments without diarrhea on the same dog (dog 3, table 3). In 2 others the periods of diarrhea were shorter by five or six days than the control period. These can hardly be considered of much significance when compared with previous experiments (Cowgill, Rosenberg and Rogoff,¹⁷ 1930) which showed that diuresis decreased the time necessary for depletion in 4 dogs from nineteen, twenty-two, thirty-three and twenty days to eight, ten, fifteen and

³⁷ Stuart, E. H., Block, R. J., and Cowgill, G. R. The Antineuritic Vitamin V. The Preparation of a Vitamin Concentrate Suitable for Parenteral Use, *J. Biol. Chem.* **105** 463-466 (June) 1934.

eleven days, respectively. It seems evident, therefore, that when the animals are not receiving vitamin B₁ by mouth and the question of failure of absorption due to diarrhea is not involved, the rate of loss of stored vitamin B₁ from the body is not accelerated by diarrhea.

In marked contrast were the results when tissue stores were lowered and daily oral doses of vitamin B₁ were administered (table 4). When mild diarrhea was induced under these conditions, without exception there was a definite increase in the amount of the vitamin required. This increase ranged from 18 to 82 per cent. It is obvious that the increase can be accounted for simply by the failure of absorption of the food materials containing vitamin B₁. It is noteworthy that the concomitant loss of part of the caloric value of the ingested food did not prevent the failure of appetite which is characteristic of vitamin B₁ deficiency.

The consistent increase in requirement seen with the daily oral doses (table 4) was absent in series 3 (table 5), in which the daily dose of vitamin B₁ was given parenterally. With the exception of dog 2, which showed a marked increase, the amounts of rice polishings concentrate needed to maintain appetite when the dogs were subjected to diarrhea were not significantly larger than those needed in the absence of diarrhea, being 0, 0, 1.2, 3.6 and 4.8 milligram equivalents per kilogram. Differences of less than 6 milligram equivalents per kilogram may be regarded as insignificant, as such a difference was found between 2 experiments on the same dog (dog 2, table 5) without diarrhea. It is apparent that the results for 5 of 6 dogs confirm those in series 1. No explanation can be offered for the anomalous behavior of dog 2.

It may be observed that the average value for the requirement of the vitamin given parenterally was 25 milligram equivalents per kilogram per day without diarrhea and, excluding dog 2, 25.5 milligram equivalents with diarrhea. The apparently lower requirement of vitamin B₁ by this route as compared to that administered orally is of little significance in view of the wide range of individual variation.

So far as the bearing of these results on the question of the excretion of vitamin B₁ is concerned, they indicate that no significant amounts of vitamin B₁ are lost by excretion into the intestinal tract when its activity is stimulated and fluid loss is encouraged by diarrhea induced with magnesium sulfate. The possibility of excretion in the bile (Muckenfuss,²² 1918) is by no means excluded. However, if these results are considered in conjunction with those obtained in 1930 (Cowgill, Rosenberg and Rogoff¹⁷), it appears probable that the chief route of excretion of vitamin B₁ is by way of the kidney.

CLINICAL APPLICATIONS

According to the previously mentioned formula (Cowgill,¹⁸ 1934) a normal person weighing 66 Kg should ingest a diet having a vitamin-

TABLE 4—*Effect of Diarrhea on Requirement of Vitamin B₁ Administered in Daily Oral Doses (Series 2)*

Dog	Source of Vitamin B ₁ *	Daily Dose								Increase			
		Without Diarrhea				With Diarrhea				Increase			
		Body Weight, Kg	Gm	Gm per Kg	Milli gram Equiv alents per Kg	Body Weight, Kg	Gm	Gm per Kg	Milli gram Equiv alents per Kg	Gm	Gm per Kg	Milli gram Equiv alents per Kg	Per cent age
1	Yeast†	10.7	2.2	0.20	23.2	11.1	3.0	0.27	31.3	0.8	0.07	8.1	17.5
2	Yeast†	8.7	1.7	0.20	23.2	More than				More than			
3	Embo‡	7.9	2.0	0.25	33.0	9.3	3.0	0.32	42.2	1.0	0.07	9.2	50.0
4	Yeast†	7.3	1.7	0.23	26.7	7.8	2.0	0.26	30.2	0.3	0.03	3.5	18.0
7	Embo‡	6.0	2.8	0.47	62.0	6.3	3.5	0.56	73.9	0.7	0.09	11.9	25.0
8	Embo‡	5.2	1.8	0.35	46.2	More than				More than			
						5.2	3.0	0.58	76.6	1.2	0.23	30.4	67.0

* For a description of these sources of vitamin B₁ see table 2

† One gram equals 116 milligram equivalents

‡ One gram equals 132 milligram equivalents

TABLE 5—*Effect of Diarrhea on Daily Parenteral Dose of Vitamin B₁ Required to Maintain Appetite in Dogs (Series 3)*

Dog	Daily Dose*								Increase			
	Without Diarrhea				With Diarrhea				Increase			
	Body Weight, Kg	Cc	Cc per Kg	Milli gram Equiv alents per Kg	Body Weight, Kg	Cc	Cc per Kg	Milli gram Equiv alents per Kg	Cc	Cc per Kg	Milli gram Equiv alents per Kg	
1	11.1	0.18	0.016	19.1	11.7	0.24	0.020	23.9	0.06	0.004	4.8	
2 (a)	9.7	0.28	0.029	34.6	10.0	0.44	0.044	52.5	0.16	0.015	17.9	
(b)	10.0	0.24	0.024	28.6	11.1	0.50	0.055	65.6	0.26	0.031	37.0	
Average				31.6				59.0			27.4	
3	9.1	0.16	0.018	21.5	9.3	0.18	0.019	22.7	0.02	0.001	1.2	
4	7.6	0.20	0.026	31.0	8.4	0.22	0.026	31.0	0.02	0.000	0	
5	9.0	0.24	0.027	32.2	8.9	0.24	0.027	32.2	0.00	0.000	0	
9	8.6	0.10	0.012	14.3	8.1	0.12	0.015	17.9	0.02	0.003	3.6	

* Rice polishings concentrate, 1 cc of which is equivalent to 1,193 milligram equivalents

calory ratio of at least 1.87. The minimum ratio for an adult weighing 35 Kg is 1 and for one of 80 Kg, 2.25. Values between 1.8 and 2 are "too close to the minimum to be satisfactory." The "average American diet" described by Sherman³⁸ (1924) has been calculated (Cowgill,³⁹

38 Sherman, H. C. Chemistry of Food and Nutrition, New York, The Macmillan Company, 1924, p. 391

39 Cowgill,¹⁸ p. 186

1934) to contain 6,847 milligram equivalents of vitamin B₁ and 2,500 calories, giving a vitamin-calory ratio of 2.74, well above the borderline for all but unusually large persons and nearly 50 per cent above the average minimum requirement.

The amount of vitamin B₁ contained in such a diet may be appreciated more readily if one considers that 6,847 milligram equivalents is equivalent to 6 cc of the rice polishings concentrate used in the animal experiments of this study or to something under 2 ounces of brewers' yeast or of wheat germ (59 and 52 Gm, respectively).

The experiments of series 2 (table 3) show that in dogs with mild diarrhea there is a rise of from 20 to 80 per cent in the daily oral requirement of vitamin B₁. This suggests that if a human being receiving an ordinary adequate diet should suffer from an analogous degree of diarrhea, his margin of safety, which would average 50 per cent, might easily be wiped out, and that if he continued to subsist on his original diet for any length of time he might be in danger of at least a mild degree of vitamin B₁ deficiency. This possibility would be increased by a change to a low residue diet which, because of the omission of many of the best sources of vitamin B₁, such as whole wheat, oatmeal, bran, nuts and many vegetables, is likely to have a vitamin-calory ratio of not more than 2.2 to 2.5. A more pronounced degree of diarrhea would still further increase the danger, and it is not difficult to see how in extreme cases the pronounced deficiency states described by Mackie⁴ (1935) and others might develop.

A calculation of the vitamin B value of the supplement recommended by Barger and Victor⁸ (1931), 200 mg of brewers' yeast three times a day, reveals that this amounts to only 69.6 milligram equivalents, which would be insignificant in supplying the needs of the individual, contributing an amount of vitamin B₁ equivalent to only 1 per cent of the "average American" daily dietary intake.

In the light of the present study some suggestions may be made in regard to the treatment of patients with chronic diarrhea. It is unwise to place much reliance on the fact that before the diarrhea developed the patient may have been in an excellent state of nutrition, for vitamin B₁ is not stored in the body in quantities sufficient to protect against the effects of prolonged deficiency. The appearance of anorexia in such cases should be regarded as a warning sign that the supply of this dietary essential which is being absorbed may be inadequate. Even for a patient whose appetite continues to be good, the diet should be planned to assure a continued intake of enough vitamin B₁.

The vitamin B₁ value of the basic diet tolerated by the patient, whether the ordinary diet to which he was accustomed before the disease became manifest or a special diet, such as one low in roughage, can

be calculated by the physician or the dietitian from tables that have been published in volumes on vitamins, by Cowgill⁴⁰ and in many handbooks of dietetics. By adding up the caloric content of the foods comprising the diet and dividing the total number of milligram equivalents of vitamin B₁ by the total number of calories, the vitamin-calory ratio can be obtained. This, of course, is of greatest value when calculated on the basis of an accurate record of the food actually ingested by the patient.

The minimum vitamin-calory ratio required by an individual, if he is an adult, depends on his body weight. The value can be calculated by the formula given previously or can be more simply found by applying the chart that has been formulated (Cowgill,⁴¹ 1934). This chart may be approximately reproduced by plotting on simple graph paper the values of the vitamin-calory ratio for body weights of 30 and 80 Kg (0.85 and 2.25, respectively) and connecting them with a straight line.

It is advised that after the minimum vitamin-calory ratio required by the patient has been ascertained and the ratio provided by the diet he is receiving has been calculated, his vitamin B₁ intake should be increased by means of some supplement, so that if the diarrhea is mild he receives a vitamin-calory ratio of at least double the calculated minimum, if the diarrhea is moderately severe the vitamin-calory ratio should be three times the minimum.

The form in which the vitamin should be provided depends on the symptoms. If the patient manifests signs of vitamin B₁ deficiency or of multiple deficiencies, it is obvious that the vitamin should be administered, along with other vitamins or any other dietary essentials indicated, in high dosage, in concentrated form and perhaps parenterally. For this purpose there are available concentrates of liver, of yeast and of rice polishings, some of which are suitable for intramuscular injection, and it is now possible to obtain the pure crystalline vitamin. In such cases the relatively high cost of these preparations is of small moment compared with the urgency of immediate administration of the vitamin in amounts large enough to have the desired therapeutic effect. Some patients in whom there is no manifest avitaminosis or in whom the only suggestion of this is some degree of anorexia may nevertheless be vomiting, or the diarrhea may be sufficiently severe so that parenteral administration may be indicated.

For the majority of patients showing diarrhea, however, it is preferable to give the extra vitamin in the form of foods rich in vitamin B₁, the most notable examples being brewers' yeast and wheat germ. Many excellent preparations of both of these materials are now on the market. In a few cases, a combination of the more rapidly acting concentrated

40 Cowgill,¹⁸ pp 87-93

41 Cowgill,¹⁸ p 110

sources and the more economical food supplements may prove most helpful. The physician should in every case prescribe products the biologic potency of which has been quantitatively determined by properly controlled animal tests.

SUMMARY AND CONCLUSIONS

The vitamin B₁ requirement of dogs with and without mild but persistent diarrhea was determined in three series of experiments. In series 1 the relative requirements were determined by observing the length of time necessary for anorexia to develop when the animals received a diet deficient in vitamin B₁ after large doses of the vitamin which permitted storage in the tissues. No significant increase in the requirement during the period of diarrhea was found by this method.

In series 2 the actual minimum oral dose needed to maintain appetite was determined. This averaged 35.5 milligram equivalents (Cowgill) per kilogram per day in the period in which there was no diarrhea. A marked increase in the daily requirement, of from 18 to 82 per cent, occurred as a result of diarrhea. The procedure in series 3 was similar to that in series 2 except that the doses were administered subcutaneously. Five of 6 dogs showed no significant increase in the requirement as a result of diarrhea. The average daily requirement of parenterally administered vitamin B₁ was 25 milligram equivalents per kilogram.

These results are interpreted to mean that failure of absorption, which would be prominent in series 2 but excluded in series 1 and 3, is the only important mechanism by which diarrhea increases the vitamin B₁ requirement. In conjunction with the previous study (Cowgill, Rosenberg and Rogoff,¹⁷ 1930), in which an enormous increase in the vitamin B₁ requirement was produced in dogs by diuresis, these experiments appear to indicate that the urinary system and not the gastrointestinal tract is the principal route of excretion of vitamin B₁.

Clinical observations by a number of authors are cited, revealing that avitaminosis, especially of the B complex, is a not infrequent complication of chronic diseases of the gastrointestinal tract in which diarrhea is a symptom. Chronic ulcerative colitis is a conspicuous example of such conditions. A plan is offered whereby the dietary management of diseases of this class with respect to the intake of vitamin B₁ can be placed on a more nearly quantitative basis than has been possible in the past.

CHANGE IN PLASMA VOLUME DURING RECOVERY FROM CONGESTIVE HEART FAILURE

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In a lecture delivered before the Royal College of Surgeons in February 1896, Starling¹ predicted on theoretic grounds that "hydiaemic plethora" must accompany congestive heart failure. Thirteen years later he was able to confirm the prediction by direct observation of a dog suffering from chronic myocardial insufficiency². By bleeding the ailing animal he recovered 500 cc of blood, as compared with 300 cc from a normal dog of the same size. In 1902 Smith,³ using the Haldane carbon monoxide inhalation method of determining the volume of the blood, demonstrated a state of plethora in a case of congestive heart failure due to an adherent pericardium. Although Bock⁴ reported finding a normal blood volume in a case of cardiac failure, more recent investigations with carbon monoxide inhalation and various dye methods⁵ have

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1 Starling, E H. Physiological Factors Involved in the Causation of Dropsy, *Lancet* **1** 1407, 1896

2 Bolton, C, and Starling, E H. Note on the Blood Pressure and Lymph Flow in a Case of Heart Disease in a Dog, *Heart* **1** 292, 1909-1910

3 Smith, L J, and McKisack, H L. On a Case in Which Cyanosis and Plethora Occurred in Association with Adherent Pericardium, *Tr Path Soc London* **53** 136, 1902

4 Bock, A V. The Constancy of the Volume of the Blood Plasma, *Arch Int Med* **27** 83 (Jan) 1921

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indicated abnormally high blood volumes for patients suffering from uncomplicated heart failure⁶. In addition, these studies have shown a decrease in blood volume during recovery from myocardial failure⁷. In spite of the agreement of the numerous independent reports, the reliability of the methods employed by these investigators has been seriously questioned⁸.

Various investigators⁹ have attempted to illuminate the problem of the blood volume in heart failure by studying the red blood cell count

6 In a small group of cases of congestive heart failure complicated by chronic pulmonary disease, Wollheim,^{5c} and Hitzengerber and Tuchfeld^{5d} found low blood volumes

7 Wollheim^{5e} Schurmeyer^{5f} Laudau and others^{5g} Levin, E. La acción inmediata de la digital sobre el volumen de la sangre circulante, *Rev Soc argent de biol* **11** 75, 1935 Mies, H. Ueber die Wirkung des Strophanthin auf die zirkulierende Blutmenge, *Ztschr f Kreislaufforsch* **23** 460, 1931

8 (a) Griesbach, W. Eine klinische brauchbare Methode der Blutmen-genbestimmung, *Deutsche med Wchnschr* **47** 1289, 1921 (b) Seyderhelm, R, and Lampe, W. Die Blutmengenbestimmung und ihre klinische Bedeutung, *Ergebn d inn Med u Kinderh* **27** 245, 1925 (c) Heilmeyer, L. Das Verhalten des Kongorots zu den Serumkolloiden, zugleich ein methodischer Beitrag zur Blutmengenbestimmung mit Kongorot nach Griesbach, *Biochem Ztschr* **212** 430, 1929 (d) Smith, H P. Determination of Plasma Volume, *J Exper Med* **51** 369, 1930, *Blood Volume Studies*, *Am J Physiol* **51** 221, 1920 (e) Graff, S, and Clarke, H T. Determination of Plasma Volume, *Arch Int Med* **48** 808 (Nov) 1931 (f) Uhlenbruck, P, and Leyendecker, T. Stufenphotometrische Blutplasmamengenbestimmungen bei Herzkranken, Normalpersonen und nach sportlichen Anstrengungen, *Ztschr f klin Med* **118** 164, 1931 (g) Brockmann, H. Ein Beitrag zur Frage der Bestimmung der zirkulierenden Blutmenge beim normalen lebenden Menschen mit der Farbstoff-Injektionsmethode, unter Benutzung des Pulfrischen Stufenphotometers, *Ztschr f d ges exper Med* **87** 208, 1933 (h) Sunderman, F W. The Measurement of Serum Volume, *J Biol Chem* **109** 1, 1935 (i) Gregersen, M I, Gibson, J J, and Stead, E A. Plasma Volume Determination with Dyes. Errors in Colorimetry, Use of the Blue Dye T-1824, *Am J Physiol* **113** 54, 1935

9 (a) Reiss, E. Die refraktometrische Blutuntersuchung und ihre Ergebnisse fur die Physiologie und Pathologie des Menschen, *Ergebn d inn Med u Kinderh* **10** 613, 1913 (b) Albrecht, C. Untersuchungen uber den Wasserwechsel im Blut bei kardialen Stauungen, *Deutsches Arch f klin Med* **171** 595, 1931 (c) Veil, W H. Ueber die klinische Bedeutung der Blutkonzentrationsbestimmung, *ibid* **112** 504, 1913, **113** 226, 1914, *Physiologie und Pathologie des Wasserhaushaltes*, *Ergebn f inn Med u Kinderh* **23** 648, 1923 (d) Nonnenbruch, W, in Bethe, A, von Bergmann, G, Embden, G, and Ellinger, A. *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1926, vol 17, p 285 (e) Beckman, K. Oedemstudien, *Deutsches Arch f klin Med* **135** 39, 1921 (f) Askanasy, S. Ueber den Wassergehalt des Blutes und Blutserums bei Kreislaufstorungen, Nephritiden, Anamien und Fieber nebst Vorbemerkungen uber die Untersuchungenmethoden und uber den Befund unter physiologischen Verhaltnissen, *ibid* **59** 385, 1897 (g) Grawitz, E. Ueber die Veranderungen der Blutmischung infolge von Circulationsstorungen, *ibid* **54** 588, 1895

and the concentration of protein in the plasma. The red blood cells were studied by the usual counting technic and the plasma protein by the refractive index method. Since there is considerable experimental error in each of these methods, it is not surprising that the results obtained were somewhat contradictory. Reiss,^{9a} for instance, found the plasma protein concentration low in congestive heart failure, while Veil^{9c} found it usually normal or slightly increased. Albrecht^{9b} and Reiss noticed an appreciable increase in the red blood cell count and the plasma protein concentration in certain cases during recovery from heart failure, whereas Veil,^{9c} Nonnenbruch^{9d} and Beckman^{9e} found little if any change.

The purpose of this paper is to report a study by more refined methods of the red blood cell count and the plasma protein concentration during recovery from congestive heart failure and to point out the relation of the observed changes to the volume of plasma.

METHODS

Changes in the number of circulating red blood cells were determined by measuring the volume of packed red blood cells. The limit of error in hematocrit measurements is definitely smaller than in the ordinary red blood cell count.¹⁰ Hemoglobin determinations and red blood cell counts were done, in addition, on many of the samples of blood. The determinations were made on oxalated blood drawn from the antecubital vein, the proper concentrations of potassium and ammonium oxalate being added to prevent any change in the size of the red blood cells.¹¹ The plasma protein concentration was measured by the macro-Kjeldahl method,¹² which is considerably more accurate than refractometer methods. The albumin-globulin ratio was determined in 4 of the 10 cases, since its value should remain constant if the changes in plasma protein concentration are due merely to loss of water from the plasma.

RESULTS

The data obtained from study of the red blood cell count, hemoglobin concentration, volume of packed red blood cells and plasma protein concentration for 10 patients recovering from congestive heart failure are tabulated in the accompanying table. Patients suffering from rheumatic, syphilitic, hypertensive and arteriosclerotic heart disease were included in the series. The initial determinations were made on the day of the patient's admission to the hospital before treatment

10 Wintrobe, M. M. Blood of Normal Young Women Residing in a Subtropical Climate, *Arch. Int. Med.* **45** 287 (Feb.) 1930.

11 Wintrobe, M. M. A Standardized Technique for the Blood Sedimentation Test, *Am. J. M. Sc.* **189** 102, 1935.

12 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, II. Methods, Baltimore, Williams & Wilkins Company, 1932, p. 698.

13 Footnote deleted on proof.

Changes in the Blood During Recovery from Congestive Heart Failure

Patient No	Initials	Age	Race	Sex	Clinical Data	Day	Reading, % Hematocrit	Erythrocytes, Million	Hemoglobin, %	Protein, Gm per 100 Cc	Albumin Globulin Ratio
1	M N	52	N	F	Arteriosclerosis, auricular fibrillation, rates, enlarged liver, moderate edema	1	44	5.0	100	5.2	66/34
						5	52	6.0	110	6.2	58/42
						17	51				
2	J E	61	W	M	Rheumatic endocarditis, auricular fibrillation, cyanosis, rates, enlarged liver, marked edema	1	46	4.5	90	5.4	
						2	47				
						6	53	6.4	120	6.2	
						10	56				
						17	56			5.7	
3	D B	39	N	M	Syphilis (?), syphilitic myocarditis, rates enlarged liver moderate edema	1	42	4.0	88	5.6	
						6	48	5.5	110	6.0	
4	W S	56	W	M	Arteriosclerosis, thyrotoxicosis auricular fibrillation rates, enlarged liver, moderate edema	1	40	4.5	90	6.1	
						4	50	6.0	100	6.9	
						24		5.4	94		
5	W H	56	N	M	Syphilitic aortitis, anasarca, enlarged liver, venous pressure, 245 mm	1	40	4.0	82	6.5	47/53
						5		5.0	110	9.1	41/59
						10	55				
						24	51	4.7	90	8.4	41/59
6	S G	44	N	M	Hypertension, arteriosclerosis, rates, moderate edema enlarged liver, venous pressure, 195 mm	1	48	5.3	108	6.3	46/54
						2	46				
						3	59	7.6	135	7.8	49/51
						4	61				
						5	61	7.8	135		
						6	62				
						9	58				
7	C B	76	W	M	Arteriosclerosis auricular fibrillation few rates slightly enlarged liver, moderate edema	1	37	3.7	82	5.9	
						4	41	3.9	88	6.1	
8	T S	48	N	M	Syphilitic aortitis rates slightly enlarged liver, moderate edema	1		3.3	77	5.4	
						4		4.5	90	6.0	
9	N B	54	W	M	Hypertension, rates enlarged liver moderate edema	1	38	4.2	79	5.1	
						2	39	4.3	83		
						3	41				
						4	43				
						5	43	4.8	94	5.2*	
10	H H	73	N	F	Hypertension auricular fibrillation rates, moderate edema enlarged liver persistent bradycardia †	1	44	5.0	100	5.2	66/34
						5	52	6.0	110	6.0	58/42
						17	51				

* Marked albuminuria was noted throughout the patient's stay in the hospital

† No digitalis was given because of persistent bradycardia Urea, caffeine citrate and ammonium chloride were administered to promote diuresis

was started. None of the patients had been taking digitalis at the time of entry, and all showed signs of failure of both the right and the left side of the heart, with moderate to marked peripheral edema. Each patient was digitalized immediately except patient 10, who because of persistent bradycardia was not given digitalis. None of the patients received diuretics (other than digitalis) except patient 10 (table).

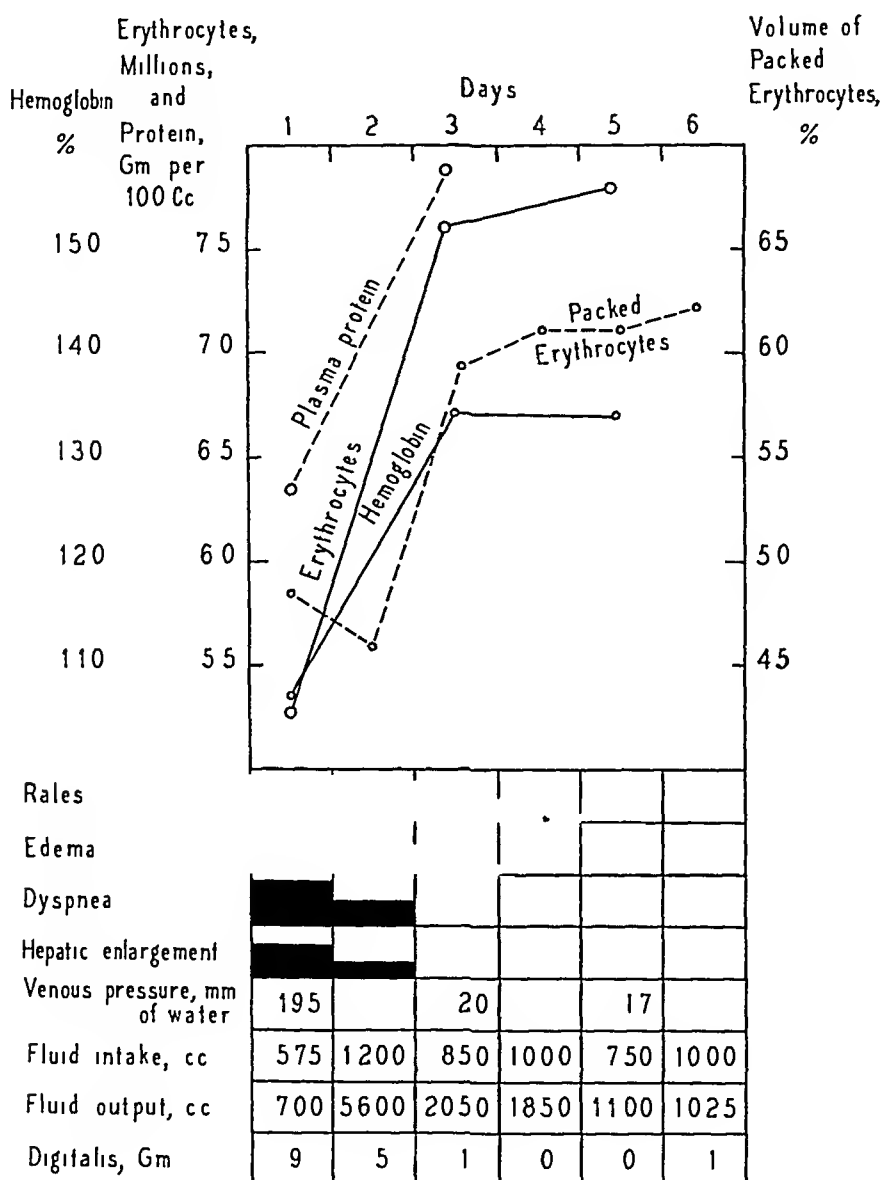


Chart 1 (patient 6) —Hemoconcentration during recovery from congestive heart failure

An analysis of the data reveals a definite rise in the concentration of hemoglobin, red blood cell count and plasma protein value during the first few days of treatment. The change in composition of the blood was observed to occur at the time of the diuresis and disappearance of edema. The data for patient 6 are plotted in chart 1.

and illustrate the magnitude of the change and the rapidity with which it may take place in certain cases Chart 2 shows the striking rise in the concentration of hemoglobin and in the red blood cell count which may occur even in spite of venesection The data for patient 10 indicate that the same changes in the blood may occur without digitalis therapy the diuresis in this case having been brought about by rest in bed and mild diuretics

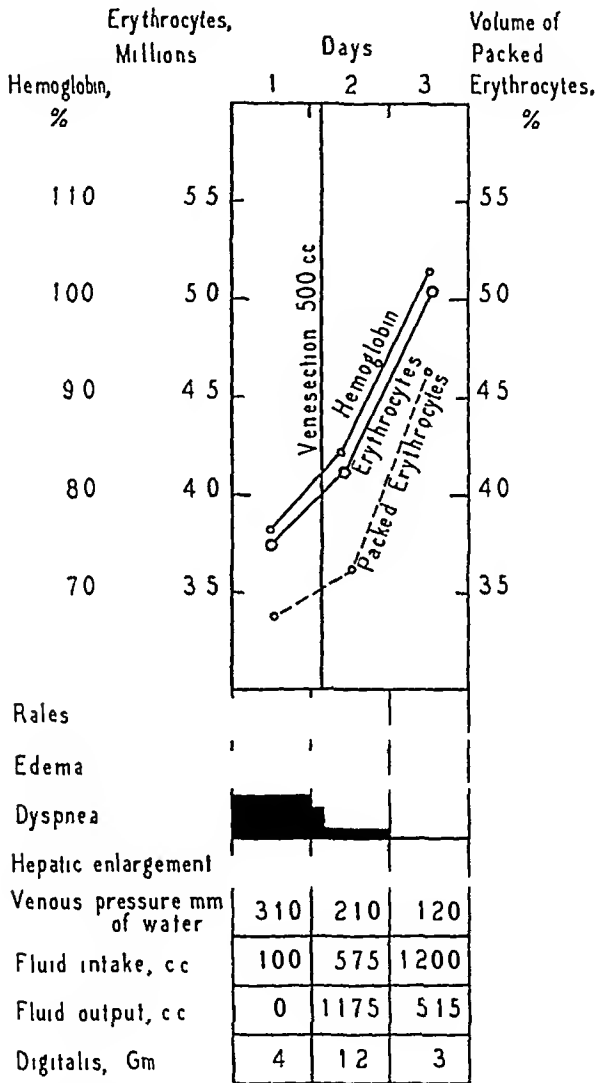


Chart 2—Chart showing the increase in the red blood cell count during recovery from congestive heart failure in spite of venesection The venous pressure on the second day was taken before venesection The fluid output for the second day includes the amount removed by venesection

COMMENT

Such marked rises in hemoglobin value, red blood cell count and volume of packed red blood cells occurring within three to six days can be explained in only two ways—either the absolute number of red

blood cells in the circulation must increase, possibly because more red blood cells are washed into the actively circulating blood stream from previously congested areas, or else the volume of the plasma must decrease, causing a concentration of the cells. That the first explanation is inadequate is obvious from the fact that there occurs a rise in the concentration of plasma protein that is roughly proportional in the majority of cases to the increase in red blood cells. An increase in the protein value cannot, of course, be accounted for by any such mechanism as that suggested in the first explanation since the protein is in solution in the plasma. The rapid proportionate increase in the red blood cell count and the plasma protein value (with the maintenance of a relatively constant albumin-globulin ratio in every case in which this factor was studied) seems to point definitely to a loss of fluid from the blood plasma.

That the plasma volume should be increased in congestive heart failure and should return to normal during recovery seems logical in view of certain well established facts relating to the pathologic physiology of cardiac insufficiency. Chronic passive congestion of the lungs, which is observed in nearly all cases of heart failure, is associated with an increase in the volume of blood in the pulmonary vascular bed as evidenced by a decrease in the patient's vital capacity¹⁴. The volume of blood in the heart and lungs has been shown by Hamilton, Moore, Kinsman and Spurling¹⁵ to be greatly increased in congestive failure, sometimes by as much as 2,000 cc. If the right ventricle as well as the left has failed, the volume of blood in the systemic venous bed likewise is increased, as evidenced in the living patient by engorgement of superficial veins, increased venous pressure and noticeable enlargement of the liver and sometimes of the spleen. The large volume of blood transferred to the pulmonary vessels and to the systemic veins is lost to the arterial circulation, and were the arterial circulation not able to compensate for the loss of blood, the patient would soon pass into a state of shock. As in the case of hemorrhage, however, the arterial blood pressure is undoubtedly maintained temporarily by a decrease in the volume of the arterial vascular bed, brought about by local vasoconstriction and more permanently by an increase in the total volume of blood resulting from retention of water in the plasma. Just as the blood of a patient suffering a large hemorrhage must become diluted, so must the plasma volume of a patient suffering from congestive heart failure be increased.

14 Harrison, T. R. *Failure of the Circulation*. Baltimore, Williams & Wilkins Company, 1935.

15 Hamilton, W. F., Moore, J. N., Kinsman, J. M., and Spurling, R. G. *Studies on the Circulation*, *Am J Physiol* 99:534, 1932.

If the water content of the plasma is increased in heart failure, there should be a decrease both in the red blood cell count and in the plasma protein concentration. Payne and Peters,¹⁶ and Herrmann,¹⁷ using the most accurate methods of measurement, have reported low plasma protein concentrations in a large series of cases of heart failure. The data given in the accompanying table also show a definite tendency toward low plasma protein values. The red blood cell data, however, as well as the data reported by Albrecht,¹⁸ Askanasy,¹⁹ Grawitz²⁰ and others, fail to show abnormally low red blood cell counts in most of the cases of congestive failure studied. This apparent discrepancy may be explained by an increase in the hemopoietic activity of the bone marrow, which raises the absolute number of red blood cells in the circulation and thereby compensates for the dilution. Evidence that the bone marrow may be stimulated is supplied by the fact that, first, polycythemia is not uncommonly observed in heart failure and, secondly, patients showing normal red blood cell counts during heart failure show marked polycythemia during recovery (patients 1 to 4, 6 and 10).

The magnitude of the changes in plasma volume indicated by the present study should be emphasized. Assuming that patient 6 (chart 1) when there was good compensation had a plasma volume of about 2.5 liters, the observed changes in the blood indicate that the plasma volume was approximately 4 liters when he was admitted to the hospital and fell roughly 1.5 liters in forty-eight hours. More important still, the rise of 1.5 Gm in the plasma protein value during the same period causes, according to Govaerts'¹⁸ data, an increase of 80 mm of water in the oncotic pressure of the plasma. As one of the most important factors in controlling the passage of water between the blood and the tissue spaces is the plasma oncotic pressure, the significance of this rise at once becomes apparent. A rise in the oncotic pressure of this order of magnitude undoubtedly plays an important part in the withdrawal of edema fluid from the tissues during recovery from heart failure and is a factor which has been almost entirely overlooked in the study of cardiac edema.

In conclusion, it should be emphasized that the method used in the present study for detecting changes in plasma volume has definite limitations. First, only the grossest change can be demonstrated by the red

16 Payne, S. A., and Peters, J. P. The Plasma Proteins in Relation to Blood Hydration, *J. Clin. Investigation* **11** 103, 1932.

17 Herrmann, G. Some Blood Chemical Findings in Congestive Heart Failure Before and After Treatment, *South. M. J.* **25** 934, 1932.

18 Govaerts, P. Influence de la teneur du serum en albumines et en globulines sur la pression osmotique des proteines et sur la formation des oedemes, *Bull. Acad. roy. de med. de Belgique* **7** 356, 1927.

blood cell and plasma protein values. For example, in patients recovering from mild heart failure, especially those with failure purely of the left side of the heart, it is often impossible to detect an appreciable change in plasma volume by this method. Secondly, the method is applicable only when the change in volume is extremely rapid, taking place within a few days. When the change occurs slowly, over weeks or months, time is allowed for complicating factors to appear which may alter the red blood cell count and plasma protein concentration directly, making interpretation of the changes in relation to plasma volume unreliable. Fortunately, a more accurate dye method has recently been perfected¹⁹ from which the sources of error inherent in the older dye methods have been eliminated. It is to be hoped that the application of this method to the study of cardiac insufficiency will result in more accurate data on plasma volume²⁰ and will lead to a clearer understanding of this important phase of the pathologic physiology of congestive heart failure.

SUMMARY

Appreciable increases in the volume of packed red blood cells, hemoglobin value, red blood cell count and plasma protein concentration have been observed for patients during recovery from severe congestive heart failure. These changes take place rapidly, within three to six days, and are interpreted as indicating a decrease in the volume of plasma. The possible relation between the decrease in plasma volume and the disappearance of cardiac edema is discussed.

19 Gregersen, Gibson and Stead⁸¹ Gibson, J. G., Jr., and Evans, W. A., Jr. Clinical Studies of the Blood Volume. I. Clinical Application of a Method of Employing the Azo Dye "Evans Blue" and the Spectrophotometer, *J. Clin. Investigation* **16** 301, 1937.

20 Since this paper was written an excellent study of the changes in the blood volume in congestive heart failure by the more accurate dye method has been published, confirming the observations here reported (Gibson, J. G., Jr., and Evans, W. A., Jr. Clinical Studies of the Blood Volume. III. Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, *J. Clin. Investigation* **16** 851, 1937).

Progress in Internal Medicine

RECENT ADVANCES IN KNOWLEDGE OF THE ANTERIOR LOBE OF THE HYPOPHYSIS

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In this, the first report on this subject to appear in the ARCHIVES OF INTERNAL MEDICINE, we wish to state the limitations we have imposed and the objective which we have set. We are not attempting a detailed review of the established knowledge in this field. This can be obtained from many volumes¹. Nor shall we attempt to quote all the pertinent literature. Abstracts may be found in the current numbers of *Endocrinology* and in the excellent annual review written by Elmer Sevringhaus in "The Year Book of Neurology, Psychiatry and Endocrinology"². The present report is not being written by or for those who are actively engaged in fundamental work in this field. Laboratory workers will find it inadequate for their purpose. It is not being written by or for those who specialize in "endocrinology."

Our aim is to record the important relations of the anterior lobe of the hypophysis for those who, like ourselves, are practicing internal

¹ From the Division of Medicine, the Mayo Clinic

1 (a) Allen, E. Sex and Internal Secretions. A Survey of Recent Research, Baltimore, Williams & Wilkins Company, 1932. (b) Kurzrok, R. The Endocrines in Obstetrics and Gynecology, Baltimore, Williams & Wilkins Company, 1937. (c) Mazer, C., and Goldstein, L. Clinical Endocrinology of the Female, Philadelphia, W. B. Saunders Company, 1932. (d) Glandular Physiology and Therapy, Chicago, American Medical Association, 1935. (e) Rolleston, H. D. The Endocrine Organs in Health and Disease, with an Historical Review, New York, Oxford University Press, 1936. (f) Cameron, A. T. Recent Advances in Endocrinology, ed 1, Philadelphia, P. Blakiston's Son & Co., 1934, ed 3, London, J. & A. Churchill, Ltd., 1936. (g) Van Dyke, H. B. The Physiology and Pharmacology of the Pituitary Body, Chicago, University of Chicago Press, 1936. (h) The Pituitary Gland. An Investigation of the Most Recent Advances, Association for Research in Nervous and Mental Disease, Baltimore, Williams & Wilkins Company, 1938, vol 17. (i) Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, Long Island, New York, The Biological Laboratory, 1937, vol 5.

2 Sevringhaus, E. L. Endocrinology. The Year Book of Neurology, Psychiatry and Endocrinology, Chicago, The Year Book Publishers, Inc., 1937.

medicine, in the broader sense of the term. In doing this we have attempted to refer to only a few "key" sources from which extensive bibliographic references may be obtained; the bibliography for this article is therefore limited.

Most of the hormonal substances which have proved of value in clinical medicine have been obtained from organs such as the pancreas, thyroid gland, sex glands and adrenal glands rather than from the anterior lobe of the hypophysis, which has an effect on all of them. Since we are discussing only the hormones of the anterior lobe of the hypophysis, we must omit mention of androgens and estrogens and certain other glandular factors. Finally we are reporting largely the accepted findings of the laboratory. The clinical application of these findings is incomplete and cannot be judged.

For many years knowledge of the anterior lobe of the hypophysis was limited to that obtained from a study of its anatomy, histology, cytology and pathology. The cytologists taught that there are three types of cells: chromophobe cells, which have no generally accepted secretory function, eosinophilic cells (a tumor of which produces acromegaly or gigantism), and basophilic cells (a tumor of which was later found by Cushing to produce the syndrome which carries his name). A new era really began when Evans and Long³ reported their work with the growth hormone in 1921. In the intervening seventeen years thousands of articles have reported work on the many hormones, real or suspected, which are attributed to the anterior lobe of the hypophysis. Separate hormones have been reported to have an effect on growth, lactation, behavior, blood, pigmentation, metabolism of carbohydrate, protein, fat and water, production of ketone bodies, and activity of the thyroid, parathyroid, pancreas, adrenal and sex glands—and this list is incomplete. When incomplete knowledge of these effects reached the ears of some indiscriminating and overly enthusiastic clinicians, there followed the publication of many more "contributions" to medical literature. It is only within recent years that a semblance of order has developed.

Even now it is not known how many hormones are produced by the anterior lobe of the hypophysis, and most certainly the clinical application of most of them is not understood. It is inconceivable that two secreting cells can produce all the hormones which have been reported. This does not mean that the anterior lobe of the hypophysis does not have many effects on the body and its metabolic processes; it indicates rather that these effects probably will be explained with fewer hormones.

3 Evans, H. M. and Long, J. A. The Effect of Feeding the Anterior Lobe of the Hypophysis on the Oestrous Cycle of the Rat. *Anat. Rec.* **21**: 62 (April) 1921.

than are required at present. Certain cytologists, notably Rasmussen⁴ and Aura Severinghaus,⁵ have offered much help. The recent studies of Severinghaus considered not only the cytology of pituitary tumors but the cytologic changes which are associated with such diseases as hypertension, nephritis, Addison's disease, tumors of the brain, diseases associated with castration and pregnancy, diseases which follow the injection of various preparations containing androgens and estrogens and those which follow thyroidectomy and artificial hyperthyroidism. In the summary he said:

Growth phenomena as seen in acromegaly and in the dwarf mice are unquestionably related to the acidophile cells. In pregnancy both the acidophiles and basophiles actively secrete. They are then jointly concerned with the reproductive phenomena involved in the pregnant state. Castration, likewise, has its effect on both cell types, although the increase of basophiles seems the more prominent alteration. This increase is associated with greater gonad-stimulating potency, and has, therefore, linked the basophile to the production of the hormone involved. It is almost certain, however, that two gonad-stimulating hormones are elaborated, and there is evidence to indicate that the acidophile may also be a source of one of these. Injections of pregnancy urine and of gonadal hormones, likewise, have their effect on both granular types of cells, although males and females do not respond similarly to all injections. This is additional evidence that both cells take part in the hypophysial control of gonad activity. Thyroidectomy and thyroid administration, likewise, affect both granular cells, and in some respects these effects are not unlike those produced by disturbances in the gonadal relationship. This not only indicates that we may not yet eliminate either cell type from thyroid relationship but it emphasizes the necessity of further study of thyroid gonadal relationships and their joint reactions with the anterior hypophysis. One should like to give way to over optimism or enthusiasm and say that with the rapid advances of experimental and cytologic researches during the last few years, the time will not be far distant when we can speak with certainty of the hormones of the anterior lobe and the cells responsible for their elaboration. When that day comes, the cytologist, at least, expects that the number of anterior lobe hormones will be much fewer than it is today, and that the varying responses of the organism will be interpreted as individual reactions to a given hormone rather than responses to individual hormones.

THE MAMMOTROPIC OR LACTOGENIC HORMONE

The rapid advance in knowledge of lactation can be illustrated by the statement that any animal equipped with nipples, whether male or

4 Rasmussen, A. T. The Proportions of the Various Subdivisions of the Normal Adult Human Hypophysis Cerebri and the Relative Number of the Different Types of Cells in Pars Distalis, with Biometric Evaluation of Age and Sex Differences and Special Consideration of Basophilic Invasion into the Infundibular Process, *A Research Nerv & Ment Dis*, Proc **17** 118-150, 1938.

5 Severinghaus, A. E. The Cytology of the Pituitary Gland, *A Research Nerv & Mental Dis*, Proc **17** 69-117, 1938, Some Aspects of Anterior Lobe Function, Suggested by a Cytological Analysis of Experimentally Altered Glands, in *Cold Spring Harbor Symposia on Quantitative Biology*,¹¹ pp 145-150.

female, can be made to lactate. This statement is startling in more ways than one, for it suggests that in the near future fatherhood may not be so simple!¹

Lactation is not the effect of a single hormone. Students of this particular problem may disagree with this brief summary, but in general it may be stated that the process occurs about as follows. First the breast must be stimulated by estrogen. Without this influence no other steps are possible. Second, in all probability the hormone of the corpus luteum further aids in the development of the breast. Nelson⁶ has emphasized the important role of the corpus luteum. Lyons'⁷ somewhat conflicting opinions can be found in his recent summary. Third, the lactogenic hormone initiates lactation, lactation is impossible without this stimulus.

Thus, in the human being development of the breast never occurs until the ovaries are functioning. Precocious development of the breasts always indicates the presence of prematurely functioning ovaries. Changes which occur in the breasts during menstruation are further evidence of the close relation which exists between the pituitary body, the ovaries and the breasts. During pregnancy a large amount of estrogen is produced, this increases the development of the breasts and opposes the production of the lactogenic hormone by the pituitary body. The sudden loss of estrogen when the placenta is expelled releases the lactogenic hormone, and lactation is initiated.

No one knows how many other glands may be indirectly concerned with the physiology of lactation. Nelson and Gaunt⁸ have enlarged on their original observation that the lactogenic hormone alone cannot initiate lactation in a hypophysectomized guinea pig, it must be combined with the hormone of the adrenal cortex. Any studies of the relation of the adrenal glands to the development of the breast and lactation are of interest to those physicians who are often puzzled by the changes in the breasts that occur in association with tumors of the adrenal glands.

Riddle and Bates⁹ and their associates at Cold Spring Harbor have

6 Nelson, W. O. Studies on the Physiology of Lactation. IV. The Assay of the Lactogenic Hormone of the Anterior Hypophysis, *Anat. Rec.* **60** 69-76 (Aug.) 1934.

7 Lyons, W. R. The Preparation and Assay of Mamotropin, in *Cold Spring Harbor Symposia on Quantitative Biology*,¹¹ pp. 198-209.

8 Nelson, W. O., and Gaunt, R. Initiation of Lactation in the Hypophysectomized Guinea Pig. *Proc. Soc. Exper. Biol. & Med.* **34** 671-673 (June) 1936, The Adrenals and Pituitary in Initiation of Lactation, *ibid.* **36** 136-138 (March) 1937.

9 Riddle, O., and Bates, R. W. Prolactin, A Research Nerv. & Ment. Dis., *Proc.* **17** 287-297, 1938. Riddle, O. Physiological Responses to Prolactin, in *Cold Spring Harbor Symposia on Quantitative Biology*,¹¹ pp. 218-228.

studied the lactogenic hormone for many years, and their list of achievements is impressive. In two recent articles Riddle reviewed his changing conceptions regarding this hormone. Originally, it was assumed to have only lactogenic and crop sac-stimulating effects. Now it is suggested that this hormone is concerned also with increasing the basal metabolic rate that it has an "antigonad" action, that it generates the brooding instinct in fowl and seems capable of inducing maternal behavior in virgin rats, that it produces splachnomegalia and increases bodily growth and that it is concerned with the metabolism of carbohydrate and fat. Needless to say, such a conception has aroused controversy, particularly when it raises doubts regarding the existence of the oldest and best established hormone, the growth hormone. Riddle expressed the opinion that too many hormones have been suggested. He said:

Much confusion has arisen in the field of pituitary physiology because too often it has been assumed that a newly observed response means a new pituitary hormone, and thereafter, instead of speaking of this response, the name of an alleged hormone has been used. In our opinion very few anterior lobe hormones have been adequately established, though it is granted that hereafter others may attain that status. But to date our diligence has been rewarded with no opportunity to examine a physiologically active preparation from anterior pituitary tissue (excluding intermedin) which did not contain effective amounts of follicle stimulating hormone, thyrotropic hormone, or prolactin, if adrenotropin is an entity, it probably could be added to this list.

The opinion of a disinterested observer might be that Riddle has not eliminated the confusion attendant on multiple hormones, he has simply transferred all the confusion to one hormone, the lactogenic hormone.

Some of this confusion may be cleared since White, Catchpole and Long¹⁰ have announced that by following the method of Lyons they have produced a crystalline protein from the pituitary body and that this protein possesses "high lactogenic activity." This is the first report of the crystallization of any hormone of the anterior lobe of the hypophysis.

The literature regarding the clinical application of this hormone is not impressive. Most reports are valueless. Kurziok and his associates,¹¹ who administered a preparation containing the lactogenic hormone to 29 patients whose supply of milk was inadequate, noted an increased production of milk in 25 instances.

Lyons¹² has described a method for assaying the amount of lactation-stimulating principle by the simple method of injecting unconcentrated

10 White, A., Catchpole, H. R., and Long, C. N. H. Crystalline Protein with High Lactogenic Activity, *Science* **86** 82-83 (July 23) 1937.

11 Kurziok, R., Bates, R. W., Riddle, O., and Miller, E. G., Jr. The Clinical Use of Prolactin, *Endocrinology* **18** 18-19 (Jan.-Feb.) 1934.

12 Lyons, W. R. Preparation and Assay of Mammatropic Hormone. *Proc. Soc. Exper. Biol. & Med.* **35** 645-648 (Jan.) 1937.

urine subcutaneously into pigeons and observing the effect on the crop glands. It is to be hoped that this test will receive wide clinical trial. The patient's urine should be subjected to this test before it is concluded that the insufficiency of the supply of milk is due to a deficiency of lactogenic hormone.

THE DIABETOGENIC HORMONE

Physicians who treat large numbers of diabetic patients are impressed with the different forms of the disease. Diabetes in a child may appear suddenly, may be severe and may be difficult to control. The mild diabetes which may be noted in the child's grandfather is as different as if it were an entirely different disease, yet both patients have diabetes. The diabetes which sometimes is associated with cerebral hemorrhage responds to the same treatment as does any other type of diabetes.

These differences and the association of diabetes with diseases of other endocrine glands have led many physicians to believe that diabetes may have multiple etiologic factors. Others believe in a unitarian cause, the lack of insulin, this belief has been recently reviewed by Wilder.¹³

The frequent association of diabetes and acromegaly has focused attention on the anterior lobe of the hypophysis. (We shall not consider the posterior lobe, although the hyperglycemic effect of pitressin is well known.) The investigator who more than any other has contributed to the knowledge of the relation of the anterior lobe of the hypophysis to carbohydrate metabolism is B. A. Houssay, professor of physiology at the University of Buenos Aires. He and his associates have reported in numerous papers the exhaustive work in progress in his laboratory. He has reported on this work in English in two rather recent articles.¹⁴ In the more recent of these he related his observations on the pituitary-carbohydrate relation to the whole problem of diabetes. He discussed the important correlation of many endocrine glands in carbohydrate metabolism—pituitary body, pancreas, adrenal glands (both the cortex and the medulla), thyroid gland and gonads.

His own contributions to the study of the important role of the anterior lobe of the hypophysis were given in more detail in the Dunham Lectures, delivered at Harvard University in 1935. He summarized his findings by stating:

Our experimental work has shown (1) In the absence of the pituitary (or of the anterior lobe) pancreatic and phlorizin diabetes is attenuated and animals retain and consume glucose. (2) Anterior pituitary lobe extract counteracts

13 Wilder, R. M. The Etiology of Diabetes, *J. Med.* **18** 275-282 (Aug.) 1937.

14 Houssay, B. A. Diabetes as a Disturbance of Endocrine Regulation, *Am. J. M. Sc.* **193** 581-606 (May) 1937, *Carbohydrate Metabolism*, *New England J. Med.* **214** 971-986 (May 14) 1936.

the action of insulin, increases pancreatic and phlorizin diabetes (3) Anterior pituitary extract can produce diabetes in normal mammals (4) When the pituitary is absent there is a tendency to hypoglycemia, hypersensitivity to insulin and other hypoglycemic agents

It is impossible to discuss Houssay's work without mentioning the work of Long and Lukens, a complete report of which is to be found in the Harvey Lectures of 1937¹⁵ The relation of the adrenal glands to carbohydrate metabolism is not properly a part of our subject, but brief mention of this relation must be made Long and Lukens demonstrated that removal of the adrenal cortex was followed by changes in the metabolism of carbohydrate which are every bit as striking as those produced by hypophysectomy and are similar in many respects Furthermore, they demonstrated that in the absence of the adrenal cortex there was no diabetogenic effect after the injection of anterior pituitary extracts Their reports have led to an interesting exchange of opinions with Houssay A disinterested observer is impressed with the excellent work of both laboratories There can be no doubt of the importance of the adrenal cortex in the intricate metabolism of carbohydrate Long has finally been able to answer the last criticism of his work by producing hyperglycemia with an extract of the adrenal cortex that was supplied by Kendall It is regrettable that space prevents a more detailed summary of the work of Houssay and of Long and Lukens

A most complete summary of this entire problem by one who is strictly impartial recently appeared In this article Russell¹⁶ discussed not only the findings of workers in this field but the theories behind such findings In her summary she said

Two principal theories have been advanced in explanation of these and related findings—one, that the anterior lobe controls gluconeogenesis from endogenous protein, if not from fat, administration of its extract causing an increase in available glucose and its removal curtailing the supply, the other theory, that the anterior lobe influences carbohydrate oxidation itself, its presence preventing carbohydrate loss below certain levels and its absence characterized by lack of restraint on carbohydrate oxidation under conditions when such would ordinarily occur Although this reviewer inclines to the latter explanation, at present it is not possible to make a final decision as to the validity or completeness of either of these theories

The final reference is to work which is of far reaching importance Young¹⁷ has been able to produce permanent diabetes in dogs after

15 Long, C N H The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, pp 194-228, *Medicine* **16** 215-247 (Sept) 1937

16 Russell, J A The Relation of the Anterior Pituitary to Carbohydrate Metabolism, *Physiol Rev* **18** 1-27 (Jan) 1938

17 Young, F G Permanent Experimental Diabetes Produced by Pituitary (Anterior Lobe) Injections, *Lancet* **2** 372-374 (Aug 14) 1937

injection of an anterior pituitary extract. Recent confirmation of this work was reported by Campbell and Best,¹⁸ who said

After the report by F. G. Young that what appeared to be a permanent diabetes may be produced in dogs by the intraperitoneal injection of certain extracts of the anterior pituitary gland, similar experiments were initiated in this department. Our findings are in accord with those reported by Young. Some of the animals failed to respond, in that diabetes did not appear. In one, a mild but constant glycosuria persisted after discontinuing the injections of the extract, in another, the sugar excretion was most irregular. In a third, an intense glycosuria persisted for a prolonged period and showed no signs of abatement. This animal was no more resistant to insulin than the average depancreatized dog. The findings with regard to the sugar excretion and sensitivity to insulin will be reported in some detail.

The importance of this accomplishment to clinical medicine is obvious, for there are many hypoglycemic states which conceivably may be due to a lack of the diabetogenic or "blood sugar raising" principle. At present no such extract is available for clinical trial.

Study of the diabetogenic hormone is interesting and important, but it should not encourage any one to abandon the accepted and successful methods of treating diabetes mellitus. One physician who has been treating diabetes and hypertension by the application of roentgen rays to the pituitary body concluded an article by saying "There is so little evidence to support the pancreatic theory of diabetes that it should be discarded." Further comment is unnecessary.

HORMONES AFFECTING THE METABOLISM OF PROTEIN AND FAT

No special discussion will be made of these "hormones," for there is insufficient evidence that individual hormones of this type exist. It is true that during the course of studies which have been referred to there is ample evidence of an effect not only on the metabolism of carbohydrate but on the metabolism of protein and fat as well. It does not logically follow that this indicates the effect of a specific hormone. The numerous papers of Anselmino and Hoffman, in which they reported the isolation of many specific metabolic hormones, including a fat metabolism or ketogenic hormone, have not received general confirmation. Thomson¹⁹ has reviewed the work on the ketogenic hormone which was done in the laboratory. He expressed the opinion that much of it will need repetition.

¹⁸ Campbell, J., and Best, C. H. Prolonged Diabetes After Administration of Extracts of the Anterior Pituitary Gland, paper presented at the meeting of the American Physiological Society, March 30-April 2, 1938.

¹⁹ Thomson, D. L. The Anterior Pituitary and the Metabolism of Acetone Bodies, *A. Research Nerv. & Ment. Dis., Proc.* **17**: 257-267, 1938.

THYROTROPIC HORMONE

The elevation of the basal metabolic rate in cases of acromegaly and its depression in cases of pituitary insufficiency have for some time suggested the presence of some hormone of the anterior lobe of the hypophysis which has an effect on and through the thyroid gland. It was hoped that such a hormone would be of value in treating certain patients who have low basal metabolic rates with or without myxedema. A review of the literature does not disclose the fulfilment of this hope. Scowen²⁰ has published an excellent article in which he proved for human beings what had been found true in experiments on animals—that the thyrotropic hormone can be expected to be of value only when the thyroid gland is normal and that it is therefore of no clinical value in cases of myxedema. Thyroid is, and probably will remain, the most effective, most easily administered and cheapest form of medicament for this disease. Scowen described the elevation of the basal metabolic rate in normal persons after the injection of a pituitary preparation containing the thyrotropic hormone and reported his ability to raise the basal metabolic rate of patients whose low rate he suspected was due to lack of thyrotropic hormone. When Collip and Anderson²¹ announced the production of an antithyrotropic serum, further hope was expressed that this substance might be of help in treating patients suffering from hyperthyroidism. This hope also has remained unfulfilled.

Uhlenhuth²² has written a thorough review of the observations made by him and others on the relation of the thyrotropic hormone to the cytology of the thyroid gland. This paper, awarded the Van Meter Prize by the American Association for the Study of Goiter, reported some interesting studies. Starr and Rawson²³ have described a quantitative method of measuring the effect of the thyrotropic hormone (the preparation administered was antuitrin-T) by measurement of the height of the acinar cells of the thyroid gland.

20 Scowen, E. F. Effects of the Thyrotropic Hormone of the Anterior Pituitary in Man, *Lancet* **2** 799-802 (Oct 2) 1937.

21 Collip, J. B., and Anderson, E. M. The Production of Serum Inhibitory to the Thyrotropic Hormone, *Lancet* **1** 76-78 (Jan 13) 1934, Studies on the Thyrotropic Hormone of the Anterior Pituitary, *J. A. M. A.* **101** 965-969 (March 23) 1935.

22 Uhlenhuth, E. The Thyreoactivator Hormone. Its Isolation from the Anterior Lobe of the Bovine Pituitary Gland and Its Effects on the Thyroid Gland, *Ann. Int. Med.* **10** 1459-1486 (April) 1937, *Tr. Am. A. Study of Goiter*, 1936, pp. 25-50.

23 Starr, P., and Rawson, R. W. A Graphic Representation of Thyroid Response to Stimulation by Thyrotropic Hormone, *Proc. Soc. Exper. Biol. & Med.* **35** 603-605 (Jan) 1937. Rawson, R. W., and Starr, P. Direct Measurement of Height of the Thyroid Epithelium. A Method of Assay of Thyrotropic Substance, Clinical Application, *Arch. Int. Med.* **61** 726-738 (May) 1938.

The opportunity to measure, by this or other methods, the amount of thyrotropic hormone which is present in different metabolic conditions should produce some interesting data. It is hoped that such studies may prove of help in the management of such puzzling conditions as the exophthalmos which progresses after thyroidectomy, recurrent exophthalmic goiter and a low basal metabolic state without myxedema.

PARATHYROTROPIC HORMONE

Not much is being written about this hormone. There are many who doubt the existence of a specific parathyrotropic hormone. Riddle and Dotti²⁴ performed some interesting experiments which seemed to throw doubt on the existence of a specific parathyrotropic hormone but which indicated some hormonal control of calcium metabolism. They found that the prolonged administration of an adequate amount of gonadotropic substance caused an increase in the amount of calcium in the serum of normal, hypophysectomized or thyroidectomized pigeons but did not have this effect when injected into castrated pigeons.

THE ADRENOTROPIC HORMONE

There really is not much to be said about this hormone, if it is a separate hormone. It is known only that the adrenal glands, in common with all other glands of internal secretion, undergo atrophy after hypophysectomy and that they can be somewhat restored by the injection of "adrenotropic hormone," which may or may not be related to the lactogenic hormone. Until purification, if possible, is complete, this hormone cannot be studied properly either in animals or in man. Gaunt²⁵ has reviewed this subject. It is evident that further work should include a detailed study of the effect of this hormone on the metabolism of the blood electrolytes, which are so typically abnormal in most cases of Addison's disease.

THE ANTERIOR LOBE OF THE HYPOPHYSIS AND WATER METABOLISM

The important relation between the posterior lobe of the hypophysis and water metabolism has long been known and has received wide clinical application in the use of pitressin in the treatment of diabetes insipidus. At the Institute of Neurology of Northwestern University Medical School, Ranson and his associates have done outstanding work in studying experimentally induced diabetes insipidus. The results of this work

²⁴ Riddle, O. and Dotti, L. B. Blood Calcium in Relation to Anterior Pituitary and Sex Hormones, *Science* **84** 557-559 (Dec. 18) 1936.

²⁵ Gaunt, R. The Adrenal-Pituitary Relationship, in *Cold Spring Harbor Symposia on Quantitative Biology* **11** pp. 395-404.

have recently been published ²⁶ A summary may be found in Ingram's article ²⁷ The important hypothalamic mechanisms which affect water metabolism are described

Richter ²⁸ has reviewed his studies on water metabolism, which have centered about the role of the anterior lobe of the hypophysis in the production of diabetes insipidus He found that the only way permanent diabetes insipidus can be produced is by allowing the anterior lobe of the hypophysis to remain His summary was as follows

1 In the rat, production of diabetes insipidus depends on the removal of the anti-diuretic hormone, pituitrin, secreted by the posterior lobe

2 The syndrome can be produced (1) by total hypophysectomy, (2) by stalk section near the brain, (3) by posterior lobectomy

3 The permanency of the symptoms depends on the presence of anterior lobe tissue and the maintenance of normal metabolism The symptoms are never permanent when all anterior lobe tissue is removed

4 The role played by the intermediate lobe has not been definitely determined

5 Polyuria is primary, polydipsia secondary

6 The maximum diuresis of diabetes insipidus is as great as the maximum diuresis produced by forcing fluids It is limited probably by the maximum capacity of the kidneys

It can be concluded that production of diabetes insipidus depends on the removal of the secretion from the posterior lobe and possibly the intermediate lobe The removal of this hormone which normally controls the secretion of urine, causes a marked diuresis This resulting dehydration in time produces drying of all membranes including those of the throat, which gives rise to an increased thirst, and an increased water intake The permanency of the increase of urine output and water-intake is dependent on the maintenance of normal metabolism as governed by secretion from the anterior lobe

This work was confirmed in its essential details by Pencharz, Hopper and Rynearson ²⁹

THE GONADOTROPIC HORMONES

A few years ago rapid advances were made in the knowledge of the relation of the anterior lobe of the hypophysis to the sex glands

26 Fisher, C, Ingram, W R, and Ranson, S W Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System, Ann Arbor, Mich, Edwards Brothers, Inc, 1938

27 Ingram, W R The Relation of the Hypophysis and Associated Hypothalamic Mechanisms to Water Exchange, in Cold Spring Harbor Symposia on Quantitative Biology,¹¹ pp 381-394

28 Richter, C P The Pituitary Gland in Relation to Water Exchange, A Research Nerv & Ment Dis, Proc **17** 392-409, 1938

29 Pencharz, R I, Hopper, J, Jr, and Rynearson, E H Water Metabolism of the Rat Following Removal of the Anterior Lobe of the Hypophysis, Proc Soc Exper Biol & Med **34** 14-17 (Feb) 1936

Briefly, knowledge was obtained of at least two gonadotropic hormones—one which was believed to be primarily follicle stimulating and one which was primarily luteinizing. A third hormone, a synergist, was described but is now rarely mentioned. The term synergism continues to apply, however, to the action which follows the injection of both the follicle-stimulating and the luteinizing fraction.

Equally serious study was given to hormones obtainable from the blood and urine of human beings and animals. Again, two hormones were found. One had a follicle-stimulating effect, it was easily obtained from the urine of castrated persons and of women past the menopause and is even now believed to be a true pituitary hormone. The other, obtained from the urine of pregnant women, from the placenta and from the blood of pregnant mares, had a luteinizing effect, and while originally it was believed to have its origin in the pituitary body, it was soon proved to be a product of the chorionic villi.

At about the same time, rapid advances were being made in studying the hormones of both the male and the female sex glands. Physicians then had preparations containing both pituitary and sex gland hormones for clinical trial, and the medical literature of that period records the beginning of the hectic race which was run, with both laboratory workers and clinicians competing. The officials of pharmaceutical houses were at their wits' ends. Here was a new field, and they were not going to be "left out." And so with laboratory workers competing for priority and with clinicians injecting large quantities of hormonal preparations of one type or another into patients suffering from a variety of conditions, the race was on. It is not over yet, but at least some laboratory workers and clinicians are beginning to slow down a little so as to catch their "second wind" and see how far they have come.

The volumes mentioned at the beginning of this article contain much helpful material, particularly the most recent publications. The best work, from the standpoint of its clinical value, lies in the field of the male and female sex glands and is not a part of this subject.

The "sex hormones" of the anterior lobe of the hypophysis are still believed to be the follicle-stimulating hormone (which also affects the germinal cells in the male) and the luteinizing hormone (which also affects the interstitial cells and the accessory sex glands in the male). Fevold,³⁰ who has done outstanding work in this field, has reviewed the subject and has defended the belief that there are two hormones. This defense has been necessary because of the belief in some quarters that there is only one gonadotropic hormone—that the different effects reported for the two hormones represent a quantitative and not a quali-

30 Hisaw, F. L., Fevold, H. L., and Greep, R. O. The Pituitary Gonadotropic Hormones, *A Research Nerv. & Ment. Dis. Proc.* **17**: 247-256, 1938.

tative difference and that if enough follicle-stimulating hormone is given, luteinization will follow. It is too early to evaluate the recent announcement by Evans, Simpson and Pencharz³¹ of a third hormone, "the interstitial cell-stimulating hormone."

Whether there are one, two or three pituitary gonadotropic hormones, the fact remains that none of them has been given an adequate clinical trial. By this we mean that there is, at present, no available commercial preparation which can be recommended as containing uncontaminated gonadotropic hormones. Our authorities are Fevold³² and Fluhmann³³. If one does not have the hormone, then surely one cannot test it, yet there are numerous articles reporting treatment with "pituitary gonadotropic hormones." Of course what is usually meant by this term is a "pituitary-like gonadotropic substance" obtained from the urine, blood or placenta of pregnant women or animals. As stated previously, this is *not* of pituitary origin. We shall appreciate correction, but we are not familiar with any commercial preparation of the gonadotropic substance in the urine of castrated subjects or of women who are past the menopause, which, as mentioned before, is almost certainly of pituitary origin.

Therefore, at this "lull in the race" we should like to suggest that if clinicians are to be expected to test pituitary gonadotropic hormones, they should be given some pure ones to use and that until they have them they cease reporting results in which they use this term. This statement does not mean that hormonal preparations obtained from other sources are not of value and should not be used, it is simply a plea for more accurate description of the material used. The "chorionic hormone" is of value in many conditions, it is not a pituitary hormone.

We cannot discuss here the many important uses of the gonadotropic hormones, except to make a plea that conservatism be used in this field as well. A few years ago the literature was crowded with reports of "100 per cent cure" of this and that. It simply was not so. Nothing is 100 per cent, and when some one reports descent of the testes within twenty minutes of the time of injection of the hormonal preparation it means one thing only—that the testes were not "undescended" in the first place. Such conservative reports as those published in a symposium

31 Evans, H. M., Simpson, M. E., and Pencharz, R. I. An Anterior Pituitary Gonadotropic Fraction (ICSH) Specifically Stimulating the Interstitial Tissue of Testis and Ovary, in Cold Spring Harbor Symposia on Quantitative Biology,¹¹ pp. 229-240.

32 Fevold, H. L. The Gonadotropic Hormones, in Cold Spring Harbor Symposia on Quantitative Biology,¹¹ pp. 93-103.

33 Fluhmann, C. F. Biologic Differences Between Anterior Pituitary Sex Hormones and Gonadotropic Substances from Pregnant Women, *A Research Nerv. & Ment. Dis., Proc.* **17** 350-360, 1938.

in 1937³⁴ should be reread. Less well considered material should not be published.

THE GROWTH HORMONE

The growth hormone is being discussed last because it was discovered first because it is the only pituitary hormone which has received extensive clinical trial and because its very existence recently has been questioned. Riddle³⁵ as mentioned in the discussion of lactogenic hormone stated the opinion that there is no growth hormone and that the growth effect is produced by a combination of lactogenic and thyrotropic hormones. His presentation of this conception has already been referred to.

Evans³⁶ has presented his answer and many physicians will wish to read his spirited reply in its entirety. There is space for only two quotations.

I now propose to test in five different ways the concept that the growth hormone is merely a mixture in certain proportions of lactogenic and thyrotropic hormones.

1 Growth hormone has been prepared remarkably high in its growth promoting values and remarkably low in the above hormones.

2 A very considerable number of hypophyseal extracts containing recognizable amounts of lactogenic and thyrotropic hormones have been studied with reference to the growth produced by them and to the quantitative relations of these two hormones. The growth effect cannot be shown to run parallel with the content of lactogenic and thyrotropic hormones or with any ratio between these two.

3 Combinations of thyrotropic and lactogenic hormones in the amounts actually present in impure but potent growth extracts produce only minimal, if any, growth effects on hypophysectomized mammals.

4 Thyrotropic and lactogenic extracts containing low but recognizable amounts of growth hormone have been administered at such high levels as to produce

34 Frank, R. T., Goldberger, M. A., Salmon, U. J., and Felshin, G. Amenorrhea. Its Causation and Treatment, *J. A. M. A.* **109** 1863-1869 (Dec 4) 1937. Burch, J. C., McClellan, G. S., Simpson, J. W., Johnson, C. D. and Ellison, E. T. The Treatment of Menorrhagia and Metrorrhagia by Endocrine Products, *ibid.* **109** 1869-1871 (Dec 4) 1937. Litzenberg, J. C. The Endocrines in Relation to Sterility and Abortion, *ibid.* **109** 1871-1873 (Dec 4) 1937. Lewis, R. M. and Adler, E. L. Endocrine Treatment of Vaginitis of Children and of Women After the Menopause, *ibid.* **109** 1873-1875 (Dec 4) 1937. Pratt, J. P., and Thomas, W. L. The Endocrine Treatment of Menopausal Phenomena, *ibid.* **109** 1875-1877 (Dec 4) 1937. Abstract of discussion on papers by Frank and others, Burch and others, Litzenberg, Lewis and Adler, and Pratt and Thomas, *ibid.* **109** 1877-1880 (Dec 4) 1937.

35 Riddle, O. Physiological Responses to Prolactin, in Cold Spring Harbor Symposia on Quantitative Biology,¹¹ pp 218-228.

36 Evans, H. M. The Hypophyseal Growth Hormone—Its Separation from the Hormones Stimulating the Thyroid, Gonads, Adrenal Cortex and Mammary Glands. *A Research Nerv. & Ment. Dis. Proc.* **17** 175-192, 1938.

slight growth Under these circumstances, a synergic action on growth of the two hormones, when administered together, could not be demonstrated

5 Not only does the claimed synergism not exist, but there is no sound biological ground for belief in the necessity of the lactogenic and thyrotropic hormones for the growth process Lactogenic preparations have now been prepared in our laboratory free of growth effects at exceedingly high levels, nor does the growth process demand thyrotropic hormone, indeed the thyroid itself may be removed, as well as the hypophysis, and excellent growth will result when growth hormone is administered to such thyroidectomized-hypophysectomized animals

In conclusion, let me repeat the assertion of my friend, Dr Oscar Riddle, "Though the concept of a growth hormone as an individual entity has been useful, it does not seem to be true" I trust that I have brought the facts we actually possess into better consonance with the demands of a "scientific conscience" by substituting for this assertion the following statements

No known mixtures of the other recognized and specific hormones of the hypophysis have as yet produced the phenomenon of general body growth so readily evoked by certain pituitary extracts Mixtures of two particular hormones which have been declared to be responsible unquestionably do not do so Growth extracts have been produced which impart a maximal growth stimulus at levels exerting no other observable effect on specific organs such as the thyroid, adrenal, mammary glands and gonads At very high levels of administration, the thyrotropic, adrenotropic, mammotropic and gonadotropic hormones are eventually demonstrable These hormones are, however, quantitatively at levels which make it wholly improbable that they play an essential role in invoking growth or in determining the degree of growth Yet even if a role were established for them, the facts as we now know them could not invalidate the conception of a growth hormone They would have no more significance than the well known need of the body, for instance, for adequate quantities of certain vitamins for growth to result No amount of these vitamins will reestablish growth in an otherwise untreated hypophysectomized animal Neither can such a creature grow with massive quantities of growth hormone if the essential vitamins be withdrawn from its diet The number of extrinsic factors essential for growth is multiple It is conceivable but not established that there is similar need for several intrinsic factors There is indubitably one essential intrinsic factor—the endocrine substance known as the hypophyseal growth hormone

In the discussion of this paper Riddle referred to additional studies which he felt that Evans had overlooked and which he believed offered convincing evidence that growth is produced by a combination of lactogenic and thyrotropic hormones He then said

Of course, the existence of an individual growth hormone would be very simply indicated if Dr Evans could hand us a preparation of "growth hormone," with proved capacity to make various suitable animals grow, and which has neither lactogenic, adrenotropic nor thyrotropic substance in it (the presence of gonad-stimulating hormone would be of little consequence) Then perhaps tomorrow I could say, "Yes, growth hormone it is" Hitherto no one has presented us with such material

To a "sideline observer" this discussion promises to be interesting

There is no doubt that extracts containing the growth hormone have had an effect when injected into patients classified as "pituitary dwarfs" (As mentioned earlier, the growth hormone is the only pituitary hormone with which clinicians have had any considerable experience) While it is true that it will add height to certain young dwarfs, there is no authenticated case on record in which a dwarf has ever been restored to normal height by the injection of any preparation of this hormone yet available

ANTIHORMONES

The last statement leads to a brief discussion of antihormones It must be brief, for Collip,³⁷ who first announced the presence of antihormones, has reviewed what is known of the entire subject in but four pages He said, in introduction

I wish it were possible in this communication to give a final answer to the vexed question as to the exact nature and significance of the anti-hormones Unfortunately it is impossible for me to do this, so I must be content with an expression of a point of view, together with a review of the recent literature on the subject I feel that the anti-hormone theory as presented in March, 1934, has been entirely justified It has been a strong directing force of the work in my own laboratory and it has been, like all theories that have been of value, a challenge to workers to devise and carry out experiments designed to verify or disprove them

Are the anti-hormones present in the blood and tissues of normal animals or are they reaction products resultant to the parenteral administration of hormone-containing extracts? When the correct answer to this question has been obtained, the problem of the anti-hormone will have been solved in large measure

The fact that inhibition of certain hormone reactions has been obtained in experimental test animals treated with the serum of certain patients is very strong evidence that the anti-hormone so demonstrated has occurred spontaneously in these individuals

It must be emphasized, however, that there are many pitfalls in such tests Inhibition of a certain hormone effect may be nonspecific The effect of the inhibitory substance may be greatly modified by the method of administration In general it is best that the hormone and the suspected antagonist be mixed *in vivo* and not *in vitro*, the injections should be made separately and at different sites, adequate control with hormone treatment only and inhibiting agent only should be run

Most of the critics of his conception of antihormones have felt that the antihormones are simply ordinary antibodies Of this he said

That true antibodies are formed in most instances in which animals are treated chronically with anterior lobe extracts containing protein which must be foreign, since the extracts are of necessity in most cases made from the glands of another species, has been proved abundantly I am, however, firmly convinced that the inhibition of either the gonadotropic or of the thyrotropic hormone by

³⁷ Collip, J B Anti-Hormones, *A Research Nerv & Ment Dis*, Proc **17** 268-275, 1938

the serum of animals rendered resistant to these hormones by prolonged treatment with unphysiologic doses is due to the presence of a true antagonizing hormone in addition to the true serological immune substance

CONCLUSIONS

Physicians who attempt to maintain a conservative and critical approach to medicine have long been disturbed by two things. First, their friends in the laboratories have seemed able to do marvelous things with the administration of various extracts to animals, and yet when patients have been treated with these extracts the results have been disappointing. Second, their enthusiastic colleagues the endocrinologists have been reporting brilliant results in all sorts of conditions, even baldness has been "curable" with a "pituitary hormone."

Now the conservative physicians feel better, for they can see a change occurring. Conservatism may yet have its "inning" in a game in which enthusiasm has been predominant. Articles are now appearing in which it is admitted that not all fat boys have "Frohlich's syndrome", that a weight reduction regimen is needed more often than a syringe of "hormone." Articles are also appearing in which many conditions described as "Simmond's disease" are correctly diagnosed as anorexia nervosa. Some writers are even stating that they do not know what is wrong with the patient.

After all, there are only a few clearcut syndromes resulting from disturbances of the anterior lobe of the hypophysis, these are dwarfism, acromegaly or gigantism, Frohlich's syndrome, Cushing's syndrome and, rarely, Simmond's disease (pituitary cachexia).

Advance will continue along two lines. First, it will be made in the laboratories. We have attempted to present some of the contributions (and confusion) to be found in the laboratory study of the anterior lobe of the hypophysis. This work is of fundamental importance and it must be encouraged in every institution in which it is in progress. Second, advance will come from the scientific application of this knowledge to patients. Splendid results have been achieved, and physicians who have adequate knowledge of endocrine products should be encouraged to treat patients whom they can study carefully and observe closely. Advancement will be halted by the continued improper publication of the results of unplanned and mismanaged treatments of patients who received unidentified preparations for undiagnosed conditions.

News and Comment

American College of Physicians—The Twenty-Third Annual Session of the American College of Physicians will be held in New Orleans, with general headquarters at the Municipal Auditorium, March 27 to 31, 1939

Dr William J Kerr, of San Francisco, is president of the college and will have charge of the program of general scientific sessions Dr John H Musser, of New Orleans, has been appointed general chairman of the session and will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the program of round table discussions to be conducted at the headquarters

International Goiter Conference—The Third International Goiter Conference, under the auspices of the American Association for the Study of Goiter, will be held in Washington, D C, Sept 12 to 14, 1938

The official language of the conference will be English Interpreters will be furnished for papers read in other languages

Papers and discussions delivered or read at the meetings are to be published in full in the form of transactions

Physicians who desire to participate in the program are requested to submit titles to Dr Allen Graham, 2020 East Ninety-third Street, Cleveland

American Congress of Physical Therapy—The seventeenth annual scientific and clinical session of the American Congress of Physical Therapy will be held cooperatively with the twenty-second annual convention of the American Occupational Therapy Association, Sept 12 to 15, 1938, at the Palmer House, Chicago Preceding these sessions, the congress will conduct an intensive instruction seminar in physical therapy for physicians and technicians, from September 7 to 10, inclusive

The program of the convention proper will include numerous special features, a variety of papers and addresses, clinical conferences and round table talks, and there will be extensive scientific and technical exhibits

The instruction seminar should prove of unusual interest to every one interested in the fundamentals and in the newer advances in physical therapy The faculty will be comprised of experienced teachers and clinicians, every subject in the field of physical therapy will be covered Information concerning the convention and the instruction seminar may be obtained by addressing the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago

Book Reviews

By-Effects in Salvarsan Therapy and Their Prevention, with Special Reference to the Liver Function By V Genner Translation from the Danish by Hans Anderson, M.D. Price, 22 kroner Pp 360 Copenhagen Levin & Munksgaard, 1936

The author, in a comprehensive and systematic study, has correlated the complications of treatment of syphilis as observed in 5,526 cases encountered in the outpatient clinic of the Rigshospital, Copenhagen, from 1913 to 1932

The material is presented in three parts. The first part is based on 148 cases of arsphenamine erythema studied in regard to the time of onset (including Milian's ninth day erythema), the amount of medication and the relation to subsequent development of jaundice, albuminuria and arthralgia. Patch and intracutaneous tests were performed on half the patients who had had arsphenamine erythema. The results of subsequent treatment of these patients with arsphenamine or bismuth are discussed. In 125 cases jaundice developed. It usually was a late manifestation, occurring after only two or more courses of arsphenamine had been given. The relation between acute jaundice from arsphenamine and epidemic jaundice is emphasized. Distinction is made between the syphilitic factor, the medicamentotoxic factor and the infectious factors. Albuminuria was seen in 176 cases and was of more frequent occurrence after treatment with arsphenamine and mercury than after the newer treatment with arsphenamine and bismuth. On the other hand, involvement of the joints did not appear until bismuth therapy was introduced.

The second part of the book is concerned with 316 outpatients who were thoroughly studied regarding subjective by-effects during one or several series of treatments. The giving of arsphenamine in concentrated solution of dextrose did away with most of the acute subjective by-effects but did not prevent the later development of jaundice and hepatitis in certain cases. In the third part of the book, correlation is made between the by-effects of arsphenamine therapy and the results of two or more types of tests of hepatic function. These were performed on 316 outpatients and on 87 patients who were hospitalized. Evidence of hepatic damage usually appeared first only some time after an intensive course of arsphenamine, but milder degrees of hepatic damage also occurred after bismuth therapy. Genner, in his conclusions, writes that "it is practical by watching for the subjective by-effects and employing the functional liver tests to differentiate those patients who are intolerant to salvarsan and to plan for them a suitable individualized treatment, so that they too may go through the salvarsan therapy without serious or permanent injury."

The last 80 pages of the book consist of reports of 146 cases of arsphenamine erythema and 125 cases of arsphenamine jaundice, together with a set of 17 elaborate tables and an adequate and pertinent bibliography. This arrangement enables the author to carry out an orderly discussion of various subjects without interruption for statement of irrelevant details in the report of individual cases. He presents a wealth of statistical data, yet in such a way that the book is easy and pleasant to read.

The translation into English is especially well done. The observations and discussions presented are essentially in accord with those reported by American syphilologists. This book represents an excellent resume of the most common complications of arsenic (arsphenamine) therapy and also of those complications arising from treatment with mercury and bismuth. Emphasis is placed on the value of tests of hepatic function. The book is to be recommended to those interested in this field of medicine.

The Thyroid and Its Diseases By J H Means, M D, Professor of Clinical Medicine, Harvard University Price, \$6 Pp 602, with 73 illustrations Philadelphia J B Lippincott Company, 1937

This book has a vivid personality It owes its origin to the Massachusetts General Hospital, and no reader can forget this fact while progressing from the title page, with its reproduction of an old print of the Bulfinch Building, to the end of the volume

The opening words of the preface introduce one to the point of view that is maintained throughout the volume "While the present work is intended to be, in a measure, a textbook of the diseases, or disorders, of the thyroid, it is in no sense an encyclopedic treatise on that subject Rather it is an account of the personal experience of a considerable group of workers in a single thyroid clinic and of the opinions and convictions derived from this experience The clinic is that of the Massachusetts General Hospital and the period of observation now extends over more than two decades"

Thus, one is given the opportunity to read, so to speak, the log of a cruise in thyrology, assembled by a group of explorers during a voyage which has lasted for approximately twenty years That the traditions of canny New England seafaring ancestors still influence the Massachusetts General Hospital Thyroid Clinic is easily perceptible, for during this voyage all available charts, in the forms of literature concerning the thyroid gland, have been consulted, and when the "M G H crew" have made soundings which have differed from those reported by other "thyroid mapmakers," these have been reported for readers to use or not, as they see fit

The charm of the book lies in the manner in which it is written It is more of a narrative than an ordinary textbook and therefore is unusually readable One follows this group of adventurers up and down the shores and rivers of the thyroid gland, and thus one is taught thyroid geography, one learns of the habits and peculiarities of folk who happen to be afflicted with thyroid disease, one hears yarns such as one sailorman might tell another about thyroid history and the rumors of thyroid territory still undiscovered, with the riches said to be hidden there, and to make the story complete, a great "Thyroid Storm" is described and how clever navigators may carefully pilot their patients through it to the shores of safety

The book is well printed and is of convenient size Beyond doubt the thyroid gland and its diseases are comprehensively discussed from a variety of points of view The literature is well assembled, and the index is carefully constructed Already one looks forward to the pleasure of reading the extensive revision of this book which the author hopes will be made in the future

Die Vitamine und ihre klinische Anwendung By W Stepp, M D, J Kuhnau, M D, and H Schroeder, M D Second edition Pp 189 Stuttgart Ferdinand Enke, 1937

This is the second edition of an excellent short book on the perplexing subject of the vitamins Of the first edition, which appeared early in 1936, *The Journal of the American Medical Association* (107 1158 [Oct 3] 1936) said, "This monograph affords an extraordinary amount of information in brief compass" This sentence well characterizes the second edition

Part of the charm of the monograph lies in its simplicity, complicated terms or descriptions are not used, and any one with the least interest in the subject can easily follow the authors' ideas The historical account of how general knowledge regarding the vitamins has grown is excellent, so is the chapter comparing vitamins and hormones The body of the book, however, runs through the vitamin alphabet, beginning with a historical account of the discovery of vitamin A, going on with something regarding its chemistry something regarding the experimental proof of its physiologic existence and a good deal regarding its clinical importance and

finally ending with a list of vitamin A preparations, with their dosage, now available for clinical use. All the other known vitamins are discussed, explained or even theorized over in similar fashion. Thus in a short book is assembled a large amount of material not only of great theoretic interest but also of considerable clinical importance.

While possibly at present some of the conclusions regarding the clinical value of certain of the vitamin preparations now on the market are not universally accepted, nevertheless the authors have been fair minded. They have put together a useful monograph that is well worth studying and that contains many stimulating ideas. It is no wonder that the first edition was promptly gobbled up, making necessary a second edition within a few months. How rapidly knowledge regarding the vitamins accumulates is well shown by the fact that, in order to be up to date and sufficiently comprehensive, the second edition is perforce fifty-nine pages longer than the first edition.

Röntgenologische und pathologisch-anatomische Studien über den tuberkulösen Primärkomplex. *Acta radiologica*, supplement 33. By J. Frimann-Dahl and Georg Waaler. Price, 9 kroner. Pp. 60, with 23 illustrations. Oslo: Nationaltrykkeriet, 1936.

This work represents a 56 page original contribution to phthisiology. Studies were made of 200 dissections, together with roentgenograms taken during life and after extirpation of the lungs. The material is analyzed for the frequency of occurrence of the primary complex, discrepancies between the clinical Pirquet test and the finding of the primary complex, the localization of the primary complex, the differential diagnosis of primary and additional infection, the visibility of the primary complex in the roentgenogram and other related problems.

The study represents a thorough investigation and supplies direct evidence regarding many controversial topics, for example, the appearance of nontuberculous calcification in the pulmonary fields in the roentgenogram and the differentiation of primary infection and reinfection.

Sero-Diagnostic Studies of Malignant Tumors. Experiments in Complement Fixation by Means of Lipoid Extracts. By Alfred Zachø. Pp. 185. Copenhagen: Levin & Munksgaard, 1936.

This is an exhaustive study of the complement fixation test for tumors. It is divided into ten chapters, each dealing with some phase of the reaction and its importance to the reaction. For one interested in working with the complement fixation test for diagnostic purposes, this monograph contains a great deal of valuable information.

The largest number of positive reactions to the complement fixation test for any one series of patients with carcinoma was only 34.2 per cent, and for some series as many as 24 per cent of the control noncancerous patients showed a positive reaction of the serum. The reactive power resides in the acetone-soluble fraction of fatty acids and particularly the cholesterol fraction. One must conclude, however, that for clinical purposes the reaction is, as yet, valueless.

Undersøgelser over en gruppe actinomyceter isolerede fra menneskets svælg. By Rigmor von Magnus. With an English summary. Paper, 6 kroner. Pp. 132. Copenhagen: Levin & Munksgaard, 1936.

This monograph deals with observations on one hundred and thirty strains of branching bacteria found in the pharynx and nasopharynx of human beings. The morphologic, biologic and serologic characteristics and pathogenicity for animals were studied. The organisms occurred in about 41 per cent of the throats examined, although they appeared to play no etiologic role in any particular disease.

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CULTURE OF HUMAN MARROW

A COMPARATIVE STUDY OF THE EFFECTS OF SULFANILAMIDE AND
ANTIPNEUMOCOCCUS SERUM ON THE COURSE OF EXPERI-
MENTAL PNEUMOCOCCIC INFECTIONS

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The pneumococcus was chosen for this study because of the great clinical importance of pneumococcic infections and because the studies that have been published have given conflicting and inconclusive results

REVIEW OF THE LITERATURE

The vaccine vial technic of culture of human marrow¹ permits quantitative studies of the interaction of living human cells and noxious and therapeutic agents. Studies of the mode of action of sulfanilamide on experimental infections due to beta hemolytic streptococci² indicated that sulfanilamide itself did not kill the organisms but rendered them vulnerable to bactericidal substances present in normal human serum probably by preventing the formation, or by neutralization, of the toxins or agglutinins of the organisms. These studies also indicated that the concentration of sulfanilamide necessary to control hemolytic streptococcic infections in the cultures was about 1/100,000 instead of 1/10,000, which had previously been recommended, and that even short periods without sulfanilamide led to rapid multiplication and the production of toxin. In the few months since that article was published much clinical evidence has accumulated to indicate that the conclusions derived from these in vitro experiments are clinically applicable. For example, from 0.3 to 0.6 Gm of sulfanilamide every four hours, day and night, has proved more effective against hemolytic streptococcic infections than a much greater daily dose of sulfanilamide given in three doses.

From the Department of Medicine and the Division of Experimental Medicine, University of Oregon Medical School

1 Osgood, E. E., and Brownlee, I. E. Culture of Human Marrow. Details of a Simple Method, *J. A. M. A.* **108** 1793 (May 22) 1937

2 Osgood, E. E. Culture of Human Marrow. Studies on the Mode of Action of Sulfanilamide, *J. A. M. A.* **110** 349 (Jan 29) 1938

A little work has been done on the action of sulfanilamide in pneumococcic infections. The *in vitro*³ studies require confirmation. Mice, rats and rabbits with pneumococcic infections have been treated with doses of sulfanilamide so large,⁴ corresponding to from 30 to 125 Gm a day for a man, that although survivals have occurred, it is difficult to see what bearing these results may have on treatment of human beings with pneumococcic infections. When doses comparable to those feasible for human beings⁵ have been used, delayed death has been the usual result. Heintzelman, Hadley and Mellon⁶ have reported a reduction in the mortality of patients with pneumonia due to type III pneumococcus from 73 per cent for the controls to 22 per cent with sulfanilamide therapy for a small series of cases, and a few other cases of recovery from pneumonia after treatment with sulfanilamide have been reported without controls.⁷ A few cases of pneumococcic meningitis have been reported in which recovery occurred⁸ after the use of sulfanilamide, although in most such cases⁹ death was only delayed. Little

3 Rosenthal, S. M. Studies in Chemotherapy. III The Effect of *p*-Aminobenzene Sulphonamide on Pneumococci *In Vitro*, Pub Health Rep **52** 192, 1937

4 (a) Rosenthal, S. M. Studies in Chemotherapy. II The Chemotherapy of Experimental Pneumococcus Infections, Pub Health Rep **52** 48, 1937. (b) Cooper, F. B., Gross, P., and Mellon, R. R. Action of *p*-Aminobenzenesulfonamide on Type III Pneumococcus Infections in Mice, Proc Soc Exper Biol & Med **36** 148, 1937. (c) Rosenthal, S. M., Bauer, H., and Branham, S. E. Studies in Chemotherapy. IV Comparative Studies of Sulphonamide Compounds in Experimental Pneumococcus, Streptococcus, and Meningococcus Infections, Pub Health Rep **52** 662, 1937. (d) Cooper, F. B., and Gross, P. Para-Aminobenzenesulfonamide Therapy in Experimental Type III Pneumococcal Pneumonia, Proc Soc Exper Biol & Med **36** 678, 1937. (e) Kreedler, W. A. Treatment of Pneumococcal Infections in Rabbits with Sulfanilamide, *ibid* **37** 205, 1937. (f) Schmidt, L. H. Use of Sulfanilamide in the Treatment of Type XIV Pneumococcus Infections in Mice, *ibid* **37** 205, 1937. (g) Buttle, G. A. H. Discussion on the Treatment of Bacterial Diseases with Substances Related to Sulphanilamide, Proc Roy Soc Med **31** 154, 1937. (h) Bauer, H., and Rosenthal, S. M. Studies in Chemotherapy. VII Some New Sulphur Compounds Active Against Bacterial Infections, Pub Health Rep **53** 40, 1938

5 Buttle, G. A. H., Parish, H. J., McLeod, M., and Stephenson, D. The Chemotherapy of Typhoid and Some Other Non-Streptococcal Infections in Mice, Lancet **1** 681, 1937

6 Heintzelman, J. H. L., Hadley, P. B., and Mellon, R. R. The Use of *p*-Aminobenzenesulfonamide in Type III Pneumococcus Pneumonia, Am J M Sc **193** 759, 1937

7 Millett, J. The Action of Sulfanilamide in a Case of Type III Pneumococcus Pneumonia, New York State J Med **37** 1743, 1937

8 Mertins, P. S., and Mertins, P. S., Jr. Meningitis Due to the Type IV Pneumococcus, with Recovery. Report of a Case, Arch Otolaryng **25** 657 (June) 1937

work has been reported on the combined use of sulfanilamide and antipneumococcus serum¹⁰

It is evident that if the value of sulfanilamide or of combinations of sulfanilamide and antiserum is to be determined by clinical investigation, a carefully controlled study of a large series of cases would have to be made, as was done in evaluating antipneumococcus serums¹¹. Such studies are practicable only in large hospitals and involve some risk for the patients who receive the therapy which ultimately proves to be unsatisfactory. It is hoped that results of investigations of marrow culture such as are reported in this article will serve as a guide to the most profitable line of clinical investigation. It remains to be seen whether the data derived from such studies will be confirmed by clinical investigation. If so, this simple and accurately controllable procedure may ultimately prove a valuable supplement to animal experimentation and clinical investigation.

METHOD

The method of culturing human marrow has been described.² Briefly, our procedure has been to introduce about 10 cc of sternal marrow into a 50 cc vaccine vial containing about 25 cc of citrated balanced salt solution. By centrifugation and removal of the buffy coat, the nucleated cells of the marrow are separated from the akaryocytes (non-nucleated erythrocytes) and diluted in a volume of marrow culture medium¹² so that the total nucleated cell count is between 1,000 and 2,000 per cubic millimeter. This culture is then brought to incubator temperature, and a suitable dilution of an actively growing virulent culture of the desired type of pneumococcus is added, the culture is thoroughly shaken and a portion is removed for the initial blood agar pour plate colony count.

9 Long, P. H. The Treatment of Certain Infections with Sulphanilamide or Its Derivatives, *Internat S Digest* **23** 259, 1937. Millett, J. The Intrathecal Use of Prontosil Soluble. Report of a Case of Type III Pneumococcus Meningitis and Septicemia Treated with Prontosil Soluble, with Complete Autopsy Report, *J A M A* **109** 2138 (Dec 25) 1937.

10 Branham, S. E., and Rosenthal, S. M. Studies in Chemotherapy. V. Sulphanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice, *Pub Health Rep* **52** 685, 1937. Gross, P., and Cooper, F. B. *p*-Aminobenzenesulfonamide and Antipneumococcal Serum Therapy in Type I Pneumococcal Infections of Rats, *Proc Soc Exper Biol & Med* **36** 535, 1937. Cooper, F. B., and Gross, P. Sulfanilamide, Antipneumococcus Serum and Vitamin C Therapy in Type II Pneumococcal Pneumonia of Rats, *ibid* **36** 774, 1937. Brown, A. E., Bannick, E. G., and Haben, H. C. The Use of Sulfanilamide and Prontosil Solution, *Minnesota Med* **20** 691, 1937.

11 Cecil, R. L., and Plummer, N. Pneumococcus Type I Pneumonia. A Study of Eleven Hundred and Sixty-One Cases, with Especial Reference to Specific Therapy, *J A M A* **95** 1547 (Nov 22) 1930. Bullowa, J. G. M., and Wilcox, C. Endemic Pneumonia. Pneumococcal Types and Their Variations in Incidence and Mortality for Adults and Children, *Arch Int Med* **59** 394 (March) 1937.

(Footnote continued on next page)

The thoroughly mixed culture is then divided into five to seven vaccine vials, 8 cc being placed in each. One of these vials is kept as a control. To the others the desired quantity of sulfanilamide or antipneumococcus serum diluted in balanced salt solution is added, and to the control an equal amount of balanced salt solution is added. The content of each vial is thoroughly mixed, and all are placed in an incubator. The time recorded is the time from the introduction of the cultures into the incubator, which is usually about fifteen minutes after the sample is withdrawn for the initial colony count. From this point on, all the cultures in one experiment are handled identically. Equal portions are removed at intervals for the making of colony counts, cell counts and smears (Wright's stain). This technic insures that all the cultures in one experiment contain the same number and type of cells, the same volume and composition of the medium and the same initial

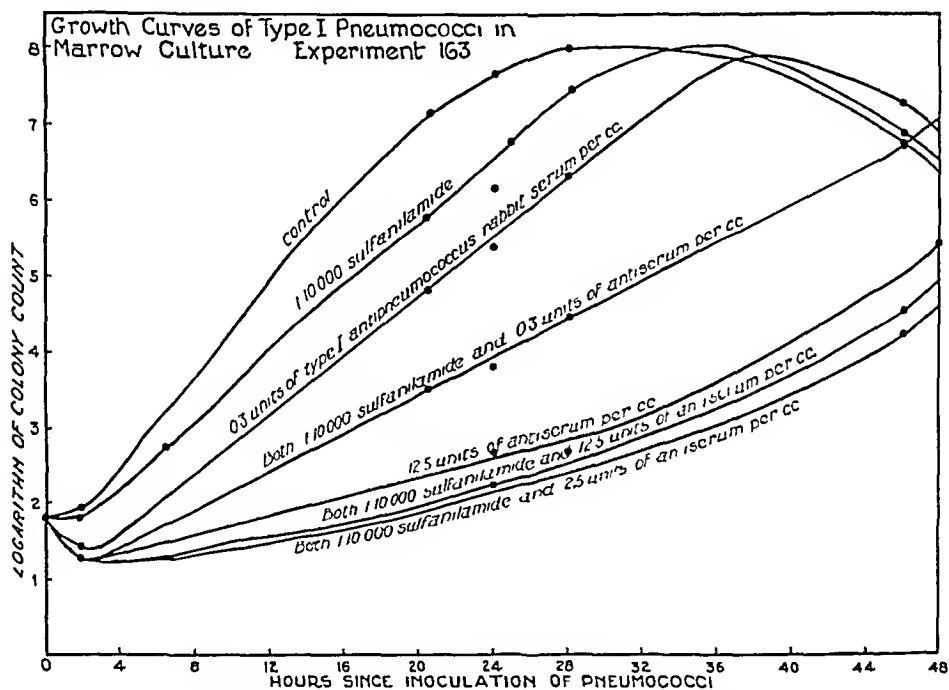


Fig 1—Logarithmic growth curves obtained in a typical experiment. By seventy hours the curve for cultures containing sulfanilamide plus 2.5 units of antiserum had risen to 600,000, and the curve for 12.5 units of antiserum plus sulfanilamide had risen to 300,000 colonies per cubic centimeter. In many of the experiments these curves decreased to zero by twelve to twenty-four hours.

inoculation of pneumococci. In other words, all factors are identical except the single variable that is purposely introduced. This is a type of control which is impossible to secure in investigations on human beings or animals.

12 This consists of 35 per cent human cord serum and the Gey and Gey (Gey, G. O., and Gey, M. K. The Maintenance of Human Normal Cells and Tumor Cells in Continuous Culture. I Preliminary Report, Cultivation of Mesoblastic Tumors and Normal Tissue and Notes on Methods of Cultivation, *Am J Cancer* 27:45, 1936) balanced salt solution or the patient's own plasma and citrated balanced salt solution.

RESULTS

Controls—The course of the growth curve in a typical experiment is shown in figure 1. In general, the larger the initial inoculation of pneumococci, the more steeply the curve rises, the earlier the peak is reached and the earlier the phase of decrease in counts begins. With the largest amount of inoculation employed, 750 organisms per cubic centimeter, a peak of about 100,000,000 was reached in sixteen hours.

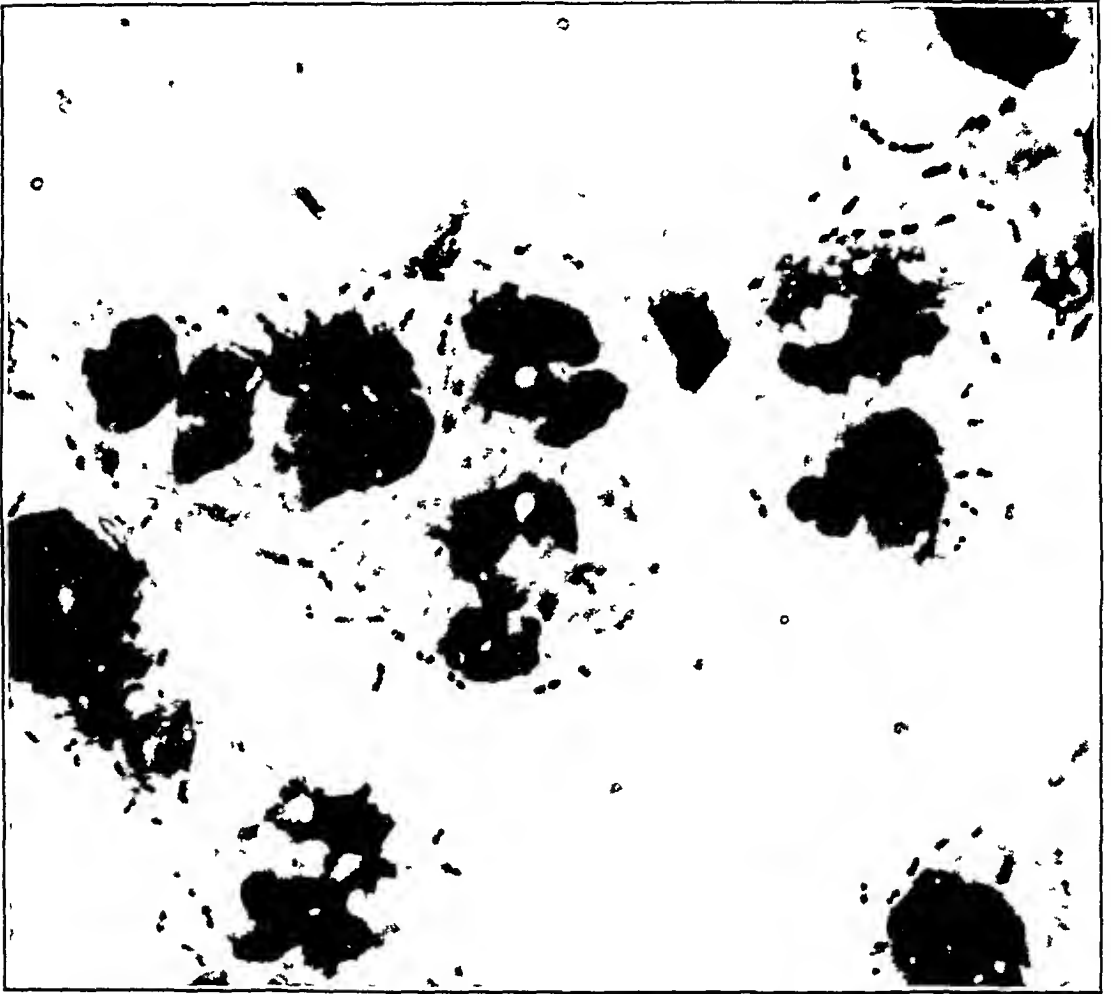


Fig 2—Photomicrograph of a smear made at nineteen hours for the control in experiment 146. The initial inoculation was of 700 type II pneumococci per cubic centimeter. Compare with figures 3 and 4. Wright's stain, $\times 2,000$.

while with inoculations of under 50 organisms per cubic centimeter, the peak was not reached for twenty-eight to thirty-two hours.

On microscopic examination the number of organisms appeared to increase even after the growth curves had begun to subside, indicating that dead organisms were visible. Smears (Wright's stain) from forty-eight to seventy-two hour cultures showed large masses of organisms and much damaged marrow cells. However, in the twenty-four hour cultures both leukocytes and erythrocytes were relatively well preserved (figs 2 and 5) in strong contrast to the picture revealed by studies of

the beta hemolytic streptococcus,² in which there was complete destruction of all marrow cells in the controls in this period

Control studies were made of pneumococci of types I, II, III and VIII and of group E (not further identified) With each, the course of the infection was much the same In most marrow cultures the pneumococci were almost entirely extracellular (fig 2), but in a few, phagocytosis occurred in the controls The phagocytosis in the controls

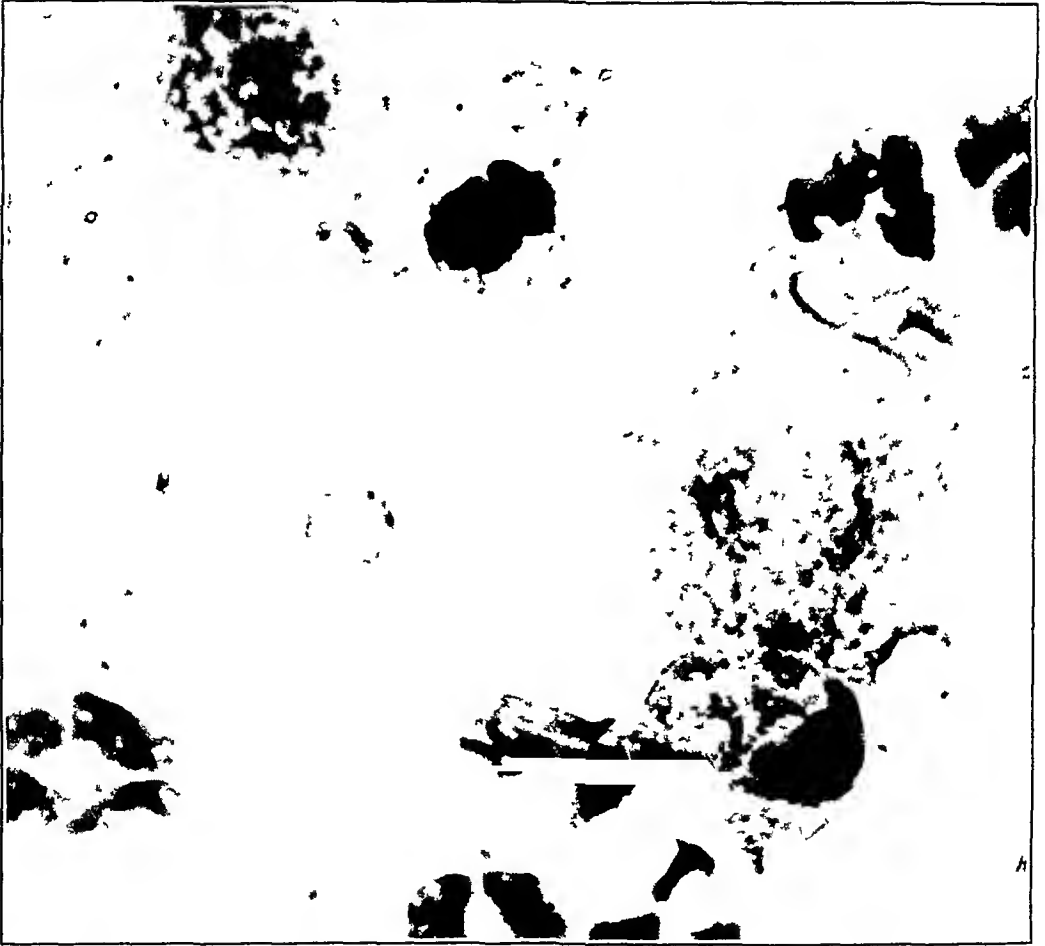


Fig 3—Photomicrograph of a smear made at nineteen hours of the culture containing 1:100,000 sulfamidamide in experiment 146 in which 700 type II pneumococci were initially inoculated Compare with figures 2 and 4 Note the absence of phagocytosis and the good structure of the marrow cells Wright's stain, $\times 2,000$

seemed to be due to a variation in the serum or plasma used for the culture medium rather than in the marrow cells In most cultures the organisms retained their typical structure and remained encapsulated In a few cases, in all of which phagocytosis occurred, there were bizarre, morphologic alterations, with little apparent effect, however, on the course of the growth curve

Sulfanilamide—In preliminary experiments 1 1,000, 1 10,000 and 1 100,000 concentrations of sulfanilamide¹³ were used in studying infections with pneumococci of types I, II, III and VIII and of group E. Bacteriostasis increased with increase in the concentration of sulfanilamide (figs 3 and 4). Thereafter, most of the experiments with sulfanilamide alone were done with the 1 10,000 concentration, since 1 100,000 was much less effective and 1 1,000, while more effective,



Fig 4—Photomicrograph of a smear made at nineteen hours from the culture containing 1 10,000 sulfanilamide in experiment 146. The initial inoculation was of 700 type II pneumococci per cubic centimeter. Compare with figures 2 and 3. No pneumococci are visible in this field, but on prolonged search through many fields occasional typical extracellular diplococci were found. Wright's stain, $\times 2,000$.

would require for human beings a dose of sulfanilamide of over 70 Gm a day, which appears to be dangerous. In all the experiments performed, comparison of smears made between twelve and twenty-eight hours showed fewer organisms and better looking cells in the cultures contain-

13 The sulfanilamide used was supplied by the Winthrop Chemical Co., Inc.

ing sulfanilamide (figs 3, 4 and 6) than in the corresponding controls (figs 2 and 5) for any type of pneumococci studied

A typical comparative growth curve is shown in figure 1. In none of the experiments, no matter how small the initial inoculation or how great the concentration of sulfanilamide up to 1:1,000, did the culture become sterile, and as far as was determined the peak was of the same general order as for the controls, but it took longer for this peak to be reached. There was no evidence of any effect of sulfanilamide on phagocytosis. If there was no phagocytosis in the control culture, there was none in the corresponding preparation containing sulfanilamide. If there was phagocytosis in the culture containing sulfanilamide, it was present in the corresponding control. The structure of the organisms appeared the same as that of the organisms in the control culture containing a corresponding number of organisms. Confirming the reports of Long¹⁴ and of Colebrook and Kenny,¹⁵ capsules were not dissolved, as has been claimed by Levaditi and Vaisman,¹⁶ nor were the capsules swollen, as they were in the cultures containing rabbit antipneumococcus serum. In other words, slight bacteriostasis was the only effect of sulfanilamide on pneumococcal infections in marrow cultures, whereas, in infections in marrow cultures due to beta hemolytic streptococci,² because of the presence of bactericidal substances in the serum used in the marrow culture medium, complete sterilization ensued. This suggests that substances bactericidal for the pneumococcus are not present in most human serums and that the effects of antipneumococcus serum in combination with sulfanilamide should be investigated. The effects of the antiserum alone also were determined to serve as a control on the effects of the two together.

Antipneumococcus Serum—The experiments with antipneumococcus serum were done with a strain of type I pneumococcus which was highly virulent for mice, since antipneumococcus serum has proved most effective clinically against type I pneumococcus. Both horse and rabbit antiserum¹⁷ were used, but no attempt was made to compare their effectiveness. All the antiserum used in any one experiment was from

14 Long, P. H., and Bliss, E. A. Para-Amino-Benzene-Sulphonamide (Sulfanilamide) or Its Derivatives in the Treatment of Infections Due to Beta-Haemolytic Streptococci, Pneumococci and Meningococci, *South M. J.* **30** 479, 1937.

15 Colebrook, L., and Kenny, M. Treatment of Human Puerperal Infections, and of Experimental Infections in Mice, with Prontosil, *Lancet* **1** 1279, 1936.

16 Levaditi, C., and Vaisman, A. Action curative du chlorhydrate de 4'-sulfamido-2,4-diaminoazobenzene et de quelques derives similaires, dans la streptococcie experimentale, *Compt. rend. Soc. de biol.* **119** 946, 1935.

17 The horse antiserum was Mulford type I, sold by Sharp and Dohme. Eli Lilly & Co. supplied the rabbit antipneumococcus serum (lot B4454) used, which is not yet available for commercial distribution.

one source. One difference noted between them was the absence with horse antiserum of the marked swelling of the capsules that was uniformly present when rabbit antiserum was used. The only other difference noted was the presence of a prozone phenomenon¹⁸ with horse antiserum so that doses above 3 units per cubic centimeter were not as effective as smaller doses, with the rabbit antiserum an increase in dose resulted in a greater ϕ , in the case of a very high dose, in an equal

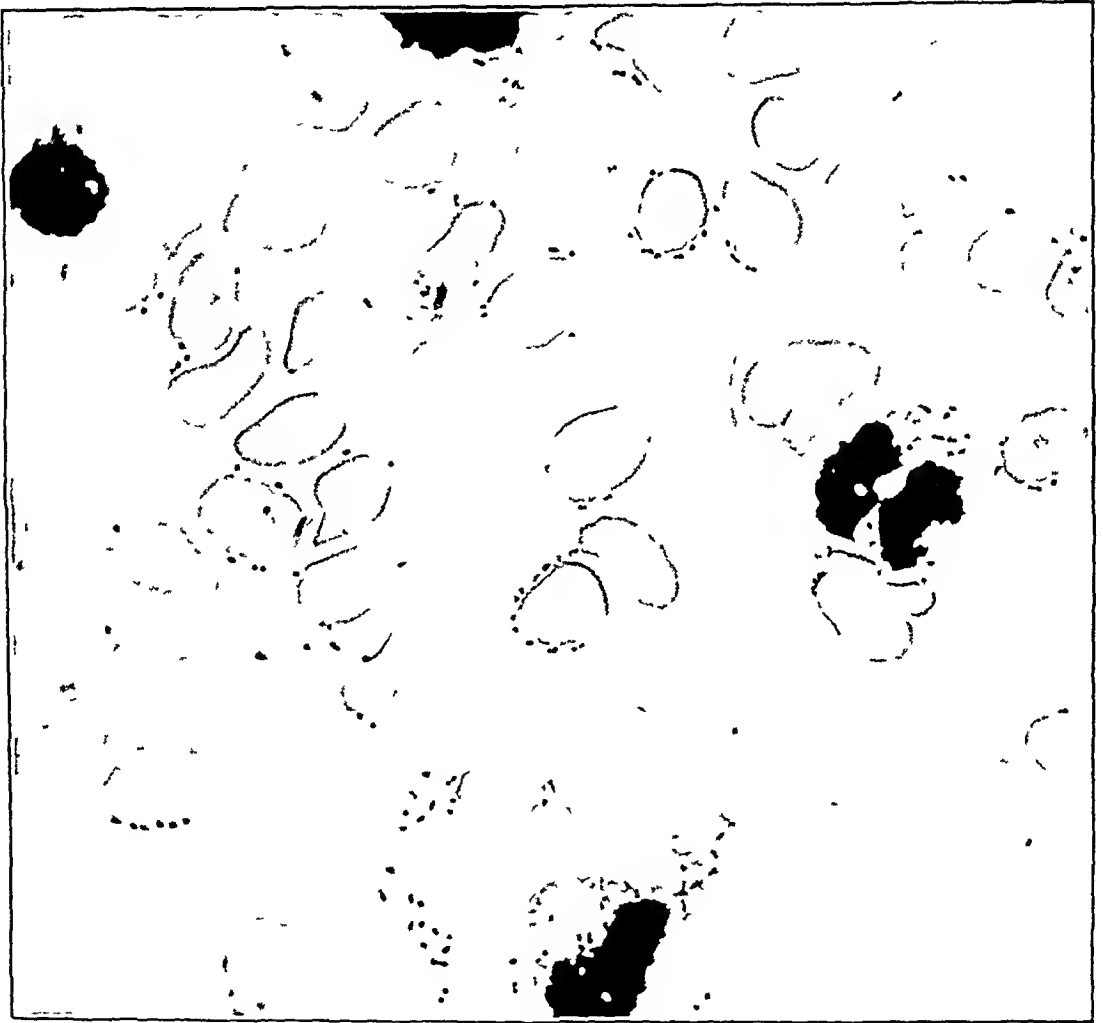


Fig 5—Photomicrograph made at twenty-fours of a smear from the control culture in experiment 158 in which the initial inoculation of type I pneumococci was 80 per cubic centimeter. Compare with figures 6 to 8. Note the large number of typical encapsulated extracellular diplococci and the slight damage to the marrow cells. Wright's stain, $\times 1,000$.

effectiveness. In all cultures containing antiserum (fig 7), even though the dose was as small as 0.03 unit per cubic centimeter, a great increase in phagocytosis was noted, few organisms being found extracellularly. This

18 Goodner, K., and Horsfall, F. L. Jr. The Protective Action of Type I Antipneumococcus Serum in Mice. I. The Quantitative Aspects of the Mouse Protection Test, *J. Exper. Med.* **62**: 359, 1935.

was most striking when there was little or no phagocytosis in the corresponding controls and in the cultures containing sulfanilamide. In the same experiment, if two different concentrations of antiserum were used, the growth curves followed each other closely for the first few hours but the curve for the culture containing the smaller concentration rose earlier. As a rule there was a definite drop in the number of organisms in the first few hours, even with the lowest concentrations, which was

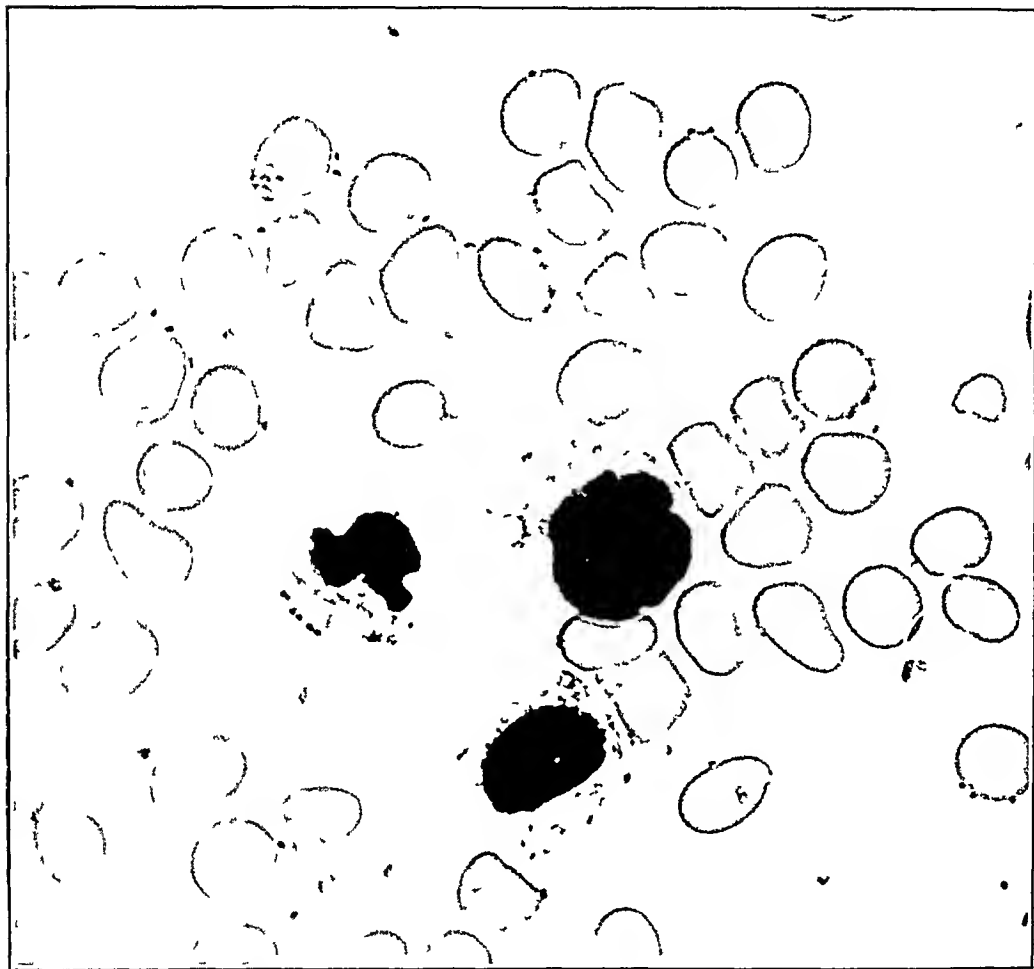


Fig 6—Photomicrograph of a smear made at twenty-four hours from the culture containing 1:100,000 sulfanilamide in experiment 158 in which the initial inoculation was of 80 type I pneumococci per cubic centimeter. Compare with figures 5, 7 and 8. Note the much smaller number of pneumococci than in the smear for the control and the extracellular position of the organisms. Note also that capsules are still present and that the structure of the marrow cells is good. Wright's stain, $\times 1,000$.

not noted for the controls or for the cultures containing sulfanilamide alone. How much of this drop was due to phagocytosis and agglutination and how much to actual killing of the organisms was not determined. The smallest quantity of antiserum used 0.03 units per cubic

centimeter of horse antiserum, had a somewhat slighter effect on the colony counts than 1 10,000 sulfanilamide in the corresponding cultures, but the next smallest dose used, 0.3 unit per cubic centimeter of horse or rabbit antiserum, was definitely more effective than 1 10,000 sulfanilamide in the corresponding cultures (fig 1). Even the highest concentration used, 50 units per cubic centimeter of rabbit antiserum, rarely sterilized cultures completely, although as a rule only a single

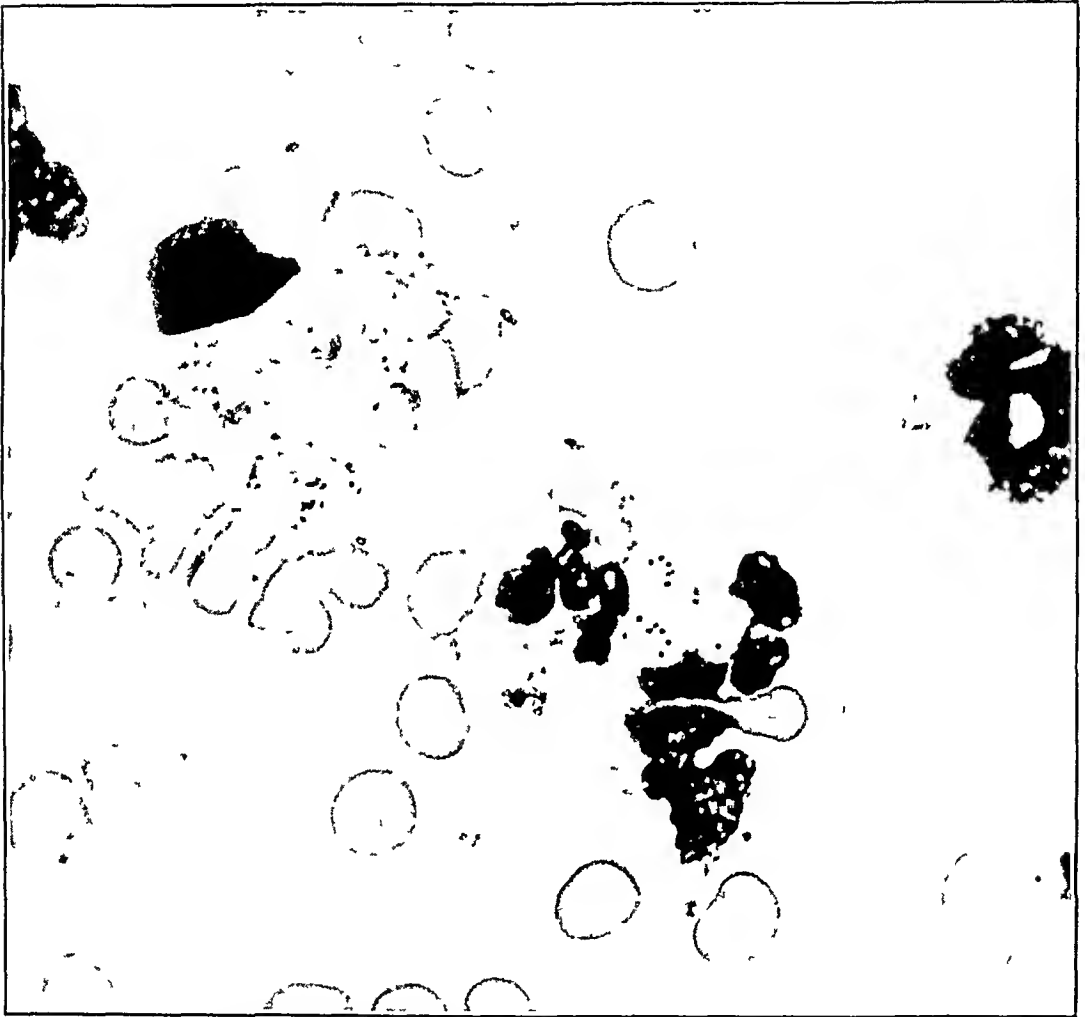


Fig 7—Photomicrograph of a smear made at twenty-four hours from the culture containing 0.6 unit of rabbit antiserum per cubic centimeter in experiment 158. The initial inoculation was of 80 type I pneumococci per cubic centimeter. Compare with figures 5, 6 and 8. Note the small number of pneumococci present, the intracellular location and the marked swelling of the capsules. A number of fields had to be examined to find any pneumococci. Wright's stain, $\times 1,000$.

colony was found occasionally in pour plates made with 0.5 cc of undiluted culture.

Concentrations of 0.3, 0.6 and 1.0 unit per cubic centimeter showed an increase in the count after the first four hours in all experiments in which they were used, the rate of increase being less for a longer period

in the cultures containing the higher concentrations. The peak colony counts for these cultures were usually lower than those reached in the corresponding control and sulfanilamide experiments, and a longer time was required to reach the peak. None of the cultures containing these concentrations became sterile. The same applied to most of the cultures with 2.5 and 12.5 units per cubic centimeter, with the exception of experiments 166 and 167, which will be discussed in detail later. For



Fig. 8—Photomicrograph of a smear made at twenty-four hours from a culture containing both 1:10,000 sulfanilamide and 0.6 unit of rabbit antiserum per cubic centimeter in experiment 158. The initial inoculation was of 80 type I pneumococci per cubic centimeter. Compare with figures 5 to 7. Note the few extracellular pneumococci with swollen capsules in the leukocyte in the center of the field. A prolonged search was necessary to find any pneumococci at all in this culture. Note also the well preserved structure of the marrow cells. Wright's stain, $\times 1,000$.

examples of the effects of various concentrations of serum alone, see figure 1 and experiments 151, 155, 164 and 165, given under the discussion concerning the use of sulfanilamide plus antiserum.

Sulfanilamide Plus Antipneumococcus Serum—In all the experiments except experiments 166 and 167, in which sulfanilamide was used in combination with antiserum, the growth curves were significantly lower than the corresponding curves for sulfanilamide alone or for the same dose of antiserum alone. Typical examples are shown in figure 1, where it will be noted that 1 10,000 sulfanilamide plus 0.3 unit of rabbit antiserum per cubic centimeter is far more effective than this concentration of either sulfanilamide or of rabbit antiserum alone and that 1 10,000 sulfanilamide plus 2.5 units of rabbit antiserum is more effective than five times as much antiserum alone. Even with the smaller doses of antiserum plus sulfanilamide the peak colony count was not nearly as high as for the corresponding cultures containing the same amount of antiserum alone, although as a rule there was no significant difference between the colony counts for the first four to six hours. The following experiments illustrate typical effects of sulfanilamide with antiserum. In all instances the organism was type I pneumococcus, and the concentration of sulfanilamide was 1 10,000. In experiments 151 and 155 horse antiserum was used, and in experiments 164 and 165 rabbit antiserum was used. The figures indicate colonies per cubic centimeter.

Experiment 151					
Hours	0	6	26		
Sulfanilamide	130	600	<1,000,000		
Antiserum, 0.03 unit per cc	130	300	600,000		
Antiserum, 0.03 unit per cc plus sulfanilamide	130	300	70,000		
Experiment 155					
Hours	0	2	24		
Control	200	250	<50,000,000		
Antiserum, 0.03 unit per cc	200	180	12,000,000		
Antiserum, 0.03 unit per cc plus sulfanilamide	200	180	700,000		
Experiment 164					
Hours	0	16	23		
Control	20	60,000,000	40,000,000		
Sulfanilamide	20	25,000,000			
Antiserum, 2.5 units per cc	20		22,000,000		
Antiserum, 2.5 units per cc plus sulfanilamide	20		1,300,000		
Antiserum, 12.5 units per cc	20		13,000,000		
Antiserum, 12.5 units per cc plus sulfanilamide	20		13,000		
Experiment 165					
Hours	0	18	24	43	70
Antiserum, 2.5 units per cc	6	2,500	30,000	175,000	100,000
Antiserum, 2.5 units per cc plus sulfanilamide	6	10	30	15	4,000
Antiserum, 12.5 units per cc	6	60	1,300	35,000	15,000
Antiserum, 12.5 units per cc plus sulfanilamide	6	20	0	0	0

For no culture with an initial count under 750 per cubic centimeter containing both sulfanilamide and antiserum in concentrations of 5 or more units per cubic centimeter was there recorded any colony count above 20,000 per cubic centimeter in the first twenty-four hours, and in the majority of instances in which 12.5 units per cubic centimeter was used, the count did not go above 100 or 200 per cubic centimeter, several being sterile with many 0.2 or 0.5 cc inoculations. However, in all cases colonies were found on pour plates made at some time between sixteen and seventy-two hours after direct inoculation with 0.5 cc.

To determine whether the action of the antiserum was specific and in order to provide further control, one experiment was performed in which the effects on the type I pneumococcus of 12.5 units per cubic centimeter of type I or type II rabbit antiserum either with or without 1:10,000 sulfanilamide were compared. The initial count was 750 per cubic centimeter. At sixteen and one-half hours the control culture showed 130,000,000, the culture containing sulfanilamide alone showed more than 500,000, that containing type I antiserum showed 28,000, that containing type I antiserum plus sulfanilamide showed 9,000, that containing type II antiserum showed more than 500,000 and that containing type II antiserum plus sulfanilamide showed 75,000 colonies per cubic centimeter. It was evident from this experiment that the type II antiserum had some effect but was far less effective than the specific antiserum, so no further work was done with type II antiserum for type I infections.

Two experiments (experiments 166 and 167) with the type I pneumococcus and rabbit antiserum gave atypical results and are reported in detail. In experiment 166, 5 indicates 1 colony from an inoculation of 0.2 cc, and 2 indicates 1 colony from an inoculation of 0.5 cc.

Experiment 166

Hours	0	4	8	12	16	20	24	48
Control	250	800	42,000	900,000	12,000,000	42,000,000	70,000,000	450,000
Sulfanilamide	250	800	36,000	700,000	2,000,000	50,000,000	72,000,000	300,000
Antiserum, 2.5 units per cc	250	30	0	5	0	0	0	0
Antiserum, 2.5 units per cc plus sulfanilamide	250	30	5	0	0	0	0	0
Antiserum, 12.5 units per cc	250	30	0	5	0	0	0	0
Antiserum, 12.5 units per cc plus sulfanilamide	250	40	40	0	5	0	0	2

Experiment 167

Hours	0	2	12	16	20	36	40	44
Control	280	350	750,000	13,000,000	?	4,000,000	1,600,000	300,000
Sulfanilamide	280	290	800,000	7,000,000	50,000,000	6,000,000	1,800,000	100,000
Antiserum, 0.3 unit per cc	280	180	4,000	20,000	200,000	50,000,000	18,000,000	2,400,000
Antiserum, 0.3 unit per cc plus sulfanilamide	280	170	3,000	12,000	75,000	?	?	6,500,000
Antiserum, 2.5 units per cc	280	150	850	300	500	170,000	650,000	800,000
Antiserum, 2.5 units per cc plus sulfanilamide	280	160	3,000	500	500	?	90,000	190,000
Antiserum, 2.5 units per cc plus 1:100,000 sulfanilamide	289	130	2,000	1,000	200	90,000	25,000	60,000

These are the only experiments in which the cultures containing sulfanilamide alone did not give lower counts than the control during the period of logarithmic growth and the only experiments in which 2.5 or 12.5 units of antiserum per cubic centimeter prevented an increase in colony count and gave results just as good as those for antiserum plus sulfanilamide. In other words, these results suggest that the serum used in making the cultures must have already contained sulfanilamide.

However, chemical examination of this serum failed to reveal any sulfanilamide, so that some other explanation must be found. It seems probable that the samples of serum from the cord must have contained a substance acting in a manner similar to that of sulfanilamide, but of course there is no way of proving this. Possibly the human serum used in the medium in these experiments was similar to blood F shown in table 1 of the study by Ward,¹⁹ already containing a high titer of substances inimical to the growth of type I pneumococci.

Hartley Broth—Since the growth curves for the pneumococcus in marrow cultures containing sulfanilamide were similar to the growth curves for the beta hemolytic streptococcus in Hartley broth containing sulfanilamide,² and since the combination of antipneumococcus serum plus sulfanilamide in marrow cultures had given results somewhat similar to those obtained with the beta hemolytic streptococcus in marrow culture medium containing human serum, it seemed desirable to study the effects of sulfanilamide plus antipneumococcus serum in Hartley broth.

Such cultures were made in Hartley broth in vaccine vials, the pneumococci being added and mixed in one vial before subdivision was made, just as in the marrow culture experiments. The results are shown in figure 9. The chief differences from the results of experiments with marrow cultures were that the growth curves ascended more steeply and reached a somewhat higher level, apparently because the medium was better adapted for the growth of the organism. There was a greater difference between the highest colony count for the cultures containing sulfanilamide alone and for the control in the broth cultures than for the marrow cultures. The difference between the colony counts for the cultures containing antipneumococcus serum and those for the controls was even more striking than for the marrow cultures with similar initial inoculations and similar concentrations of antiserum. Concentrations as low as 2 units of rabbit antiserum per cubic centimeter produced complete sterility on pour plates made from 1 cc. of the undiluted culture in several cultures with less than 500 pneumococci per cubic centimeter in the initial inoculation. None of the Hartley broth cultures in which horse antiserum was used became sterile, probably because of the prozone phenomenon, but only a few experiments were made, and either a very small dose, 0.03 unit per cubic centimeter, or a very large dose, 50 units per cubic centimeter, was employed.

In all instances in which the cultures did not become sterile too soon for the difference to be detected, a significantly lower count was found

19 Ward, H. K. Observations on the Phagocytosis of the Pneumococcus by Human Whole Blood. I. The Normal Phagocytic Titre and the Anti-Phagocytic Effect of the Specific Soluble Substance, *J. Exper. Med.* **51** 675, 1930.

for the cultures containing both antipneumococcus serum and 1 10,000 sulfanilamide than for the corresponding cultures containing antiserum alone. As in the marrow culture experiments with the pneumococci, 1 100,000 sulfanilamide in combination with antiserum was found much less effective than the 1 10,000 concentration. Many more experiments of this type must be made before extensive conclusions are justified, but these results seem sufficiently consistent to warrant their preliminary publication.

COMMENT

These results indicate that in marrow cultures, sulfanilamide alone produces only slight slowing of the rate of multiplication of pneumo-

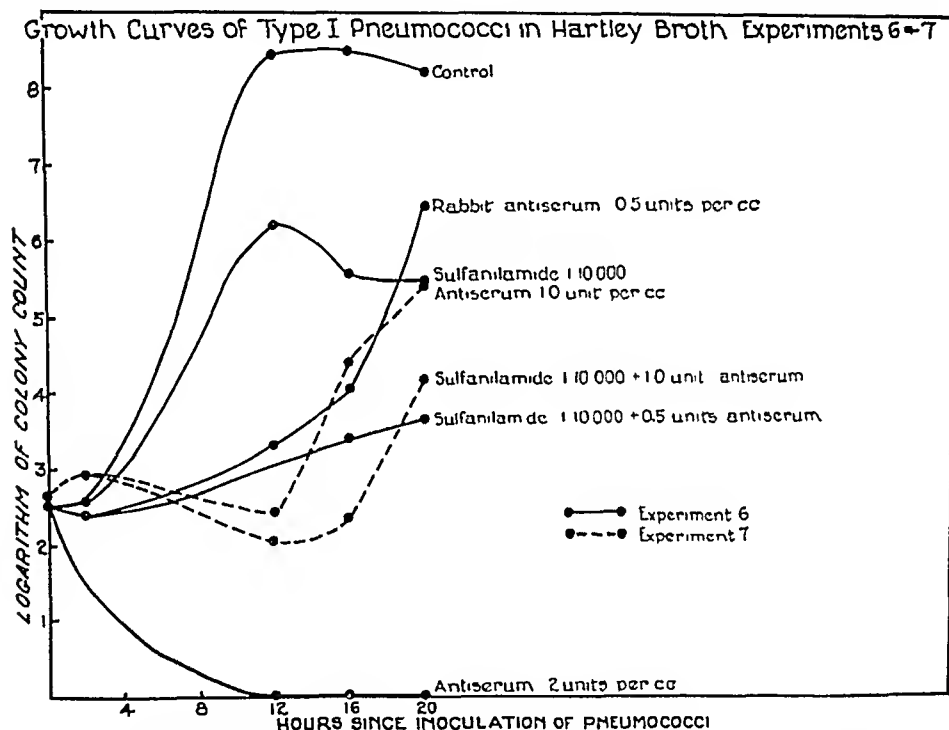


Fig 9—Logarithmic growth curves for experiments 6 and 7, in which Hartley broth was used. The data for experiment 6 are shown completely with the exception of the two curves determined for 2 units of rabbit antipneumococcus serum plus 1 10,000 and 1 100,000 sulfanilamide, which were not significantly different from the curves for 2 units alone. In experiment 7 the curves for the control and for the culture containing sulfanilamide have been omitted, since they almost exactly paralleled the corresponding curves for experiment 6.

cocci, similar to that which has been repeatedly demonstrated with sulfanilamide for other organisms²⁰ in ordinary bacteriologic mediums.

20 Long, P. H., and Bliss, E. A. Para-Amino-Benzene-Sulfonamide and Its Derivatives. Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcal Infection, a Preliminary Report, J. A. M. A. 108:32 (Jan 2) 1937. Osgood.²

This explains why treatment with sulfanilamide only delays the death of animals, such as the mouse, which show a practically 100 per cent mortality for untreated pneumococcic infections. Even small concentrations of antipneumococcus serum are more effective in marrow cultures or in broth than sulfanilamide in 1:10,000 concentration, but unless the dose of antiserum is not so great as to produce sterility by itself, the use of sulfanilamide with antiserum is more effective than the use of either alone. The production of sterility in broth cultures of pneumococci indicates that the action of rabbit antipneumococcus serum is not due entirely to its effect on phagocytosis and that the antiserum must contain some bactericidins or bacteriolysins. These results together with those previously published² suggest that the important variable in the effectiveness of sulfanilamide in different mediums or animals and against different organisms is the presence or absence of substances bactericidal for that micro-organism in the culture medium or in the body fluids of the particular human being or animal. Just how sulfanilamide renders the micro-organism more susceptible to the action of bactericidal substances is not yet known with certainty, but this work suggests that its effect on the production of toxins or agglutinins is more important than its bacteriostatic activity and that it has little direct influence on phagocytosis.

For human beings who have some resistance to pneumococci one might expect from these results that sulfanilamide would somewhat improve the mortality over that obtained without antiserum, but when antiserum is available it is so much superior that there is no clinical justification for using sulfanilamide alone. It is also evident that the larger the dose of sulfanilamide, the better the results, but there are now enough data on the toxicity of sulfanilamide to make it doubtful whether doses equivalent to the 1 to 1.5 Gm. per kilogram used in some animal experiments²¹ would be safe for administration to human beings. These results also suggest that sulfanilamide given with the present large doses of antiserum may appreciably lower the mortality or that sulfanilamide given in conjunction with a smaller amount of antiserum than is now used should give an equally low mortality at less expense.

Not enough clinical investigation has been done to furnish any statistical value, but we know of 4 cases of type I lobar pneumonia in which treatment with large doses of antiserum and sulfanilamide was given as a result of these studies. All the patients were afebrile within twenty-four hours and were able to leave the hospital within four to seven days after the onset of the illness. Two patients with type III pneumonia recovered after the administration of large doses of sulf-

21 Rosenthal^{4a} Cooper, Gross and Mellon^{4b} Rosenthal, Bauer and Branham^{4c} Kreidler^{4e} Schmidt^{4f} Bauer and Rosenthal^{4h}

anilamide alone²² It is evident that in a large series of cases carefully controlled studies should be made, the use of antiserum alone being alternated with the use of antiserum plus sulfanilamide Should such studies indicate that the investigations here recorded on experimental infections in human marrow cultures are applicable to clinical infections, this method will have been demonstrated to be a useful adjunct to animal experimentation and clinical investigation

SUMMARY

Culture of human marrow makes possible a type of control not attainable in animal experimentation or in clinical investigation In human marrow cultures, sulfanilamide exhibits a slight bacteriostatic action on pneumococcic infections which is increased by an increase in concentration Even 0.3 unit per cubic centimeter of specific antipneumococcus serum is more effective against the type I pneumococcus than is sulfanilamide alone Sulfanilamide plus any given dose of antiserum less than the amount which will by itself reduce colony counts to nearly zero is more effective than corresponding doses of antiserum alone These effects do not depend chiefly on phagocytosis The results support the view that sulfanilamide renders the organism more vulnerable to bactericidal substances present in the serum If the results of these in vitro experiments on the interaction of therapeutic and noxious agents in the presence of living human cells are applicable to infections in human beings, sulfanilamide therapy should be of value in pneumococcic pneumonia and might delay death in pneumococcic meningitis, but it will not prove as effective as even small amounts of type-specific antiserum If used in conjunction with antiserum it should further lower the mortality with the present doses of antiserum or should give an equally low mortality with smaller doses of antiserum The use of both sulfanilamide and therapy designed to introduce or develop specific bactericidins should be investigated further as a possibly effective treatment for infections which are relatively resistant to the action of sulfanilamide alone

²² These cases were reported in a personal communication from Dr J V Straumfjord, Astoria, Ore, and Dr W C Hunter, Portland, Ore

HYPERPARATHYROIDISM DUE TO IDIOPATHIC HYPERTROPHY (HYPERPLASIA ?) OF PARATHYROID TISSUE

FOLLOW-UP REPORT OF SIX CASES

FULLER ALBRIGHT, M D

HIRSH W SULKOWITCH, M D

AND

ESTHER BLOOMBERG, B S

BOSTON

In 1934 the first paper on this subject from the clinic of the Massachusetts General Hospital was published¹ In that report three cases of hyperparathyroidism, from a series of nineteen cases of the condition in which the diagnosis was proved by operation, were cited in which pathologic examination showed what was then termed diffuse hyperplasia of all parathyroid tissue, rather than one or more circumscribed adenomas It was pointed out that these cases represented a separate disease entity Since that time the total number of cases of proved hyperparathyroidism at the Massachusetts General Hospital has increased to thirty-five, and the number of cases of "hyperplasia" has increased to six As far as we are aware, a diagnosis of hyperplasia has not been made during life in other clinics, and these six patients remain a unique group This paper is a follow-up report of the six cases Some of the questions which could not be answered at the time of the first publication can now be disposed of, others remain completely obscure

For those not familiar with the earlier publications it should be emphasized again that the histologic picture of the parathyroid glands in these cases is entirely different from that seen in cases of compensatory hyperplasia of parathyroid tissue, e g, with long-standing renal insufficiency, rickets osteomalacia or pregnancy² By "compensatory hyperplasia" is meant the condition encountered in cases in which there

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From the Medical Service of the Massachusetts General Hospital and the Department of Medicine, Harvard Medical School

1 Albright, F, Bloomberg, E, Castleman, B, and Churchill, E D Hyperparathyroidism Due to Diffuse Hyperplasia of All Parathyroid Glands Rather Than Adenoma of One, *Arch Int Med* 54 315 (Sept) 1934

2 Albright, F, Drake, T G, and Sulkowitch, H W Renal Osteitis Fibrosa Cystica, *Bull Johns Hopkins Hosp* 60 377, 1937

is an increased need for the hormone if the calcium level of the serum is to be maintained at a normal value. By "idiopathic hyperplasia" is meant the condition here under discussion, in which some influence is apparently driving the parathyroid tissue to produce more hormone than is required, with resulting hypercalcemia and all the sequelae of primary hyperparathyroidism. The hyperthyroidism of exophthalmic goiter is a somewhat analogous example, wherein a condition other than neoplasia gives rise to more hormone than is needed.

Two interesting questions were brought up in the first paper concerning this disease. The first was academic and still remains a question. It concerns the nature of the influence causing the changes in the parathyroid glands. As previously pointed out, there seemed considerable circumstantial evidence to suggest an overabundance of a pituitary parathyrotropic factor. Some observations have been made which do not substantiate or disprove this possibility. These will be discussed after the clinical data have been given.

The second question was a practical one and one which fortunately can now be answered explicitly. The question arose whether it would be possible to effect a permanent cure by operation. In the earlier paper this aspect of the problem was summed up in the following statement:

If it is learned by experience that there is a certain fixed amount of hyperplastic tissue which can be left in place—too little to regenerate and again cause hyperparathyroidism, but sufficient to prevent the parathyreoprivic state—then, and only then, will the condition be amenable to surgical treatment.

There was another question embodied in this part of the problem—whether the influence causing the pathologic condition of the parathyroid tissue was a permanent one. The disquieting thought occurred that a patient might have sufficient parathyroid tissue removed to cause a return to the isoparathyroid state, while the remaining tissue stayed abnormal, however, such a patient might find himself in a serious situation if the underlying influence causing the pathologic condition of the parathyroid tissue corrected itself in the course of time.

REPORT OF CASES ³

CASE 15 ^{3a}—A more complete history is given in a previous article ¹. In brief, the diagnosis of hyperparathyroidism was first made in November 1933, when the patient, a widow of 62, entered the hospital for the third time with the diagnosis of renal calculi. She had been passing gravel for seven years, so that it is fair

3 The number of the case refers to the series of cases of proved hyperparathyroidism studied at the Massachusetts General Hospital, the same numbering being used in all publications. This particular case was referred to in various articles.

3a Albright, Bloomberg, Castleman and Churchill ¹. Albright, Aub and Bauer ⁸. Churchill and Cope ^{9a}. Castleman and Mallory ^{9c}.

to assume that the condition was present at least seven years before her admission to the hospital in 1926. The menopause occurred in 1923. There was no evidence of osseous disease in 1933, which agreed with the finding of an only slightly elevated phosphatase level of the serum. Renal function was only slightly impaired,

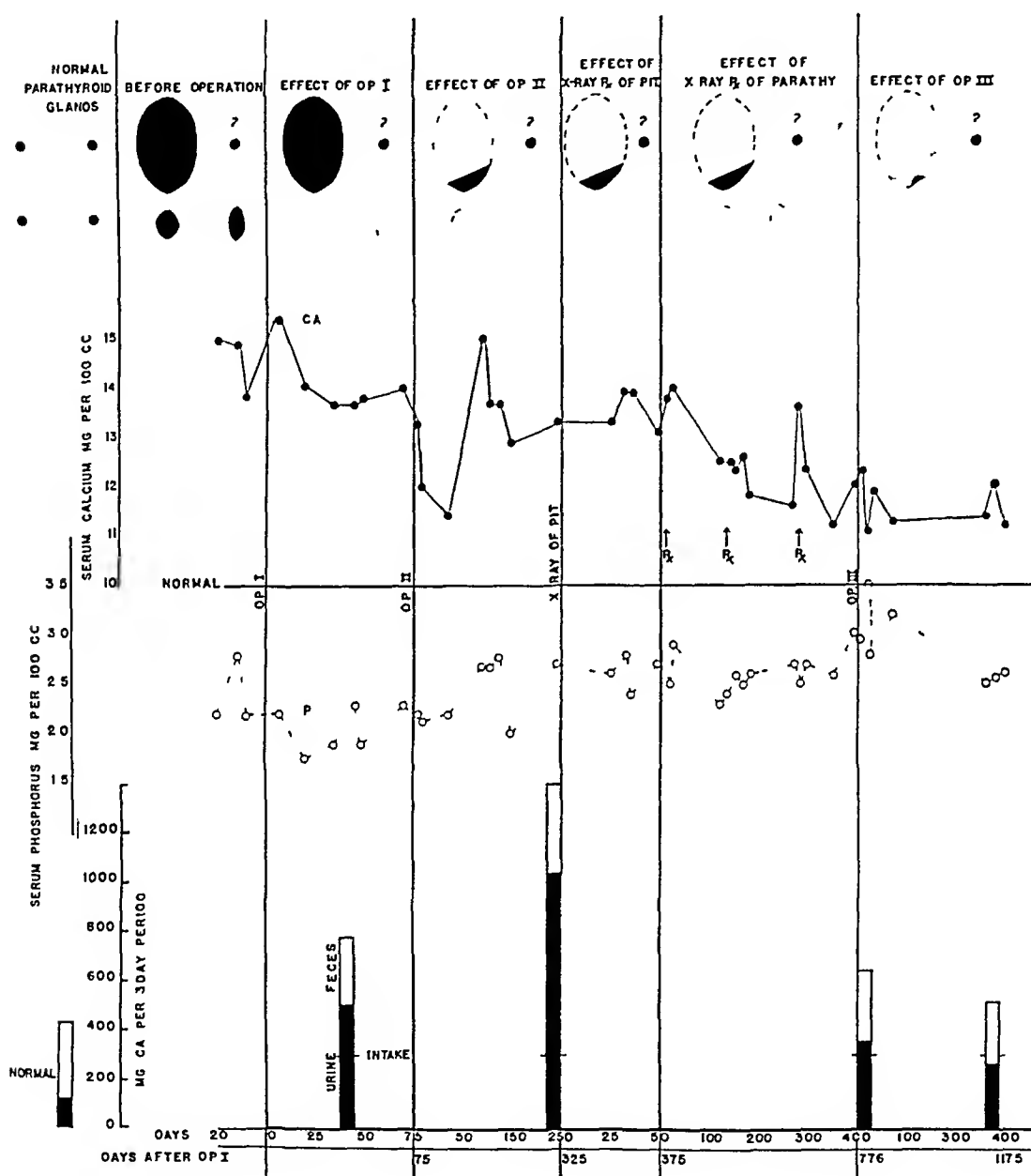


Fig 1 (case 15) —Diagram showing the effect of various therapeutic procedures on the degree of hyperparathyroidism, as judged by the serum calcium and inorganic phosphorus levels and the excretion of calcium. One gland was never seen and is depicted as a gland of normal size and marked with a question mark. Note that it was not until after the third operation that the condition was brought under control.

and there was no retention of nonprotein nitrogen. She had, in addition, rheumatic heart disease, with mitral stenosis and auricular fibrillation.

In figure 1 the initial calcium and inorganic phosphorus values of the serum are recorded, together with the effect of various therapeutic procedures on these

values In December 1933 Dr Edward D Churchill removed both lower enlarged parathyroid glands These measured 1.5 by 1.2 by 0.5 cm and 1.8 by 0.8 by 0.6 cm, respectively, and together weighed 1,100 mg This procedure had no effect on the degree of hyperparathyroidism, as judged by the serum calcium and phosphorus values and the metabolic data (fig 1 and table)

At a second operation, in February 1934, Dr Churchill found a large right upper parathyroid gland (5.0 by 3.0 by 1.3 cm) weighing 10,000 mg but could not find the left upper parathyroid gland He resected the gland, leaving behind a piece with an estimated weight of 500 mg (four normal parathyroid glands weigh about 150 mg) This second procedure was followed by only transient improvement of the blood values

In July 1934 it was decided to try large doses of estrogenic substance The thought behind this was as follows As pointed out in the previous paper, there was considerable indirect evidence that the underlying disorder might be an excess of a pituitary parathyrotropic hormone This patient's condition came on at about the time of the menopause, when there starts an increased functioning of the follicle-stimulating hormone of the anterior lobe of the pituitary body It seemed possible that the hypothetic parathyrotropic hormone might be either identical with the follicle-stimulating hormone or, what was more probable, influenced by the same factors Several of the pituitary hormones are decreased by treatment with estrogenic substance follicle-stimulating hormone,⁴ diabetogenic hormone⁵ and growth hormone⁶ Hence 600 rat units of estradiol⁷ was given three times daily for twenty-three days The serum calcium and phosphorus values remained unaltered (fig 1) After cessation of this treatment there was vaginal bleeding, as was to be expected from such large doses of estrogenic substance In the light of more recent studies we believe that the amount of treatment may have been too little to return the follicle-stimulating hormone level to normal Some data with larger doses of estrogen in the form of estradiol benzoate were obtained at a much later date which rather indicated that the serum calcium level was decreased with this therapy (table)

In accordance with the same line of reasoning irradiation of the pituitary gland was given early in December 1934 The patient received 800 roentgens to each side of the skull, focused on the pituitary body This procedure was again without effect on the abnormal calcium and phosphorus values of the serum (fig 1)

In January 1935 it was decided to try irradiation over the parathyroid tissue left in place at the second operation Reports have appeared in the literature of cases in which supposed hyperparathyroidism has been "cured" by irradiation of the cervical region Experience from this clinic has made it clear that such

4 Albright, F, and Halsted, J A Studies on Ovarian Dysfunction II The Application of the "Hormonal Measuring Sticks" to the Sorting Out and to the Treatment of the Various Types of Amenorrhoea, *New England J Med* **212** 250 (Feb 7) 1935

5 Barnes, B O, Regan, J F, and Nelson, W O Improvement in Experimental Diabetes Following the Administration of Amniotin, *J A M A* **101** 926 (Sept 16) 1933

6 Zondek, B The Inhibitory Effect of Follicular Hormone on the Anterior Lobe of the Pituitary Gland, *Lancet* **1** 10 (Jan 4) 1936

7 The estradiol used in these investigations was supplied by Dr Gregory Stragnell and Dr Erwin Schwenk, of the Schering Corporation, Bloomfield, N J

Metabolic Data in Case 15

Date of Periods (Inclusive)	Period	Calcium, Gm per Day			Phosphorus, Gm per Day			Serum Calcium, Mg per 100 Ce	Serum Phos- phorus, Mg per 100 Ce	Rat Units of I ¹³¹ radio- Benzene per Period		
		Urine	Feces	Intake	Balance	Urine	Feces				Intake	Balance
1934												
After first opera- tion and before second operation	Jan 14 to 16	1	0.18	0.09	0.10	-0.17	0.34	0.07	0.46	+0.05		
	Jan 17 to 19	2	0.17	0.11	0.10	-0.21	0.27	0.17	0.46	+0.02		
	Jan 20 to 22	3	0.17	0.09	0.10	-0.16	0.29	0.10	0.46	+0.07	1.9	
1934												
After second operation	Nov 23 to 25	1	0.35	0.11	0.10	-0.39	0.61	0.20	0.79	-0.22	2.7	
	Nov 26 to 28	2	0.35	0.10	0.10	-0.15	0.50	0.25	0.59	-0.16		
1936												
Directly after blind operation, effect of inges- tion of calcium lactate	Mar 16 to 18	1	0.13	0.05	0.10	-0.08	0.41	0.23	0.79	-0.08	3.0	
	Mar 19 to 21	2	0.12	0.09	0.10	-0.11	0.45	0.22	0.79	-0.08		
	Mar 22 to 24	3	0.11	0.15	0.10	-0.16	0.33	0.17	0.59	+0.09		
	Mar 25 to 27	4	0.13	0.16	0.17	+0.18	0.30	0.17	0.79	+0.12	3.5	
	Mar 28 to 30	5	0.15	0.21	0.47	+0.15	0.32	0.20	0.79	+0.07		
	Mar 31 to Apr 2	6	0.10	0.23	0.17	+0.08	0.37	0.22	0.79	+0.00	2.8	
1937												
Final observa- tion and effect of estrogenic substance	Mar 13 to 15	1	0.10	0.08	0.10	-0.08	0.37	0.17	0.79	+0.05		
	Mar 16 to 18	2	0.10	0.10	0.10	-0.10	0.35	0.20	0.79	+0.04	2.6	
	Mar 19 to 21	3	0.07	0.08	0.10	-0.05	0.38	0.16	0.79	+0.05	2.5	
	Mar 22 to 24*	4	0.09	0.08	0.10	-0.07	0.36	0.21	0.79	+0.02	20,000	
	April 1 to 3	5	0.07	0.10	0.10	-0.07	0.31	0.25	0.79	+0.00	10,000	
	April 4 to 6	6	0.07	0.09	0.10	-0.06	0.35	0.25	0.79	-0.02	10,000	
	April 7 to 9	7	0.07	0.04	0.10	-0.01	0.32	0.11	0.79	+0.16	10,000	

* Metabolic studies were discontinued for one week as the patient contracted a cold

treatment is ineffective in cases of parathyroid adenoma⁸. It seemed possible, however, that it might be effective in cases of so-called parathyroid hyperplasia. The patient had her first treatments on January 17 and 19. At this time she received 400 roentgens. The treatment had to be interrupted, however, because of an attack of acute cholelithiasis. On January 20 Dr. Joe V. Meigs performed cholecystostomy and removed about twenty stones from the gallbladder. (Incidentally, these stones contained almost no ash, so that it is unlikely that the hyperparathyroidism had anything to do with them, as, for instance, by increasing the calcium content of the bile.) The patient made an uneventful recovery. It should be noted, however, that the presence of mild diabetes first became apparent at this time. The course of irradiation was completed in May and June, when she received an additional 800 roentgens to the remainder of the right upper parathyroid gland. There was no immediate change in the serum calcium and phosphorus values. She returned in October and received further irradiation. This time it was given on both sides of the neck, on the basis that a fourth parathyroid tumor might have been overlooked. She received 900 roentgens over each of two fields measuring 10 by 10 cm. on either side of the neck. This treatment gave her a sore throat, but the hyperparathyroidism remained the same.

Finally, since it was realized from observations in other cases that too much tissue had been left behind at the second operation, even on the assumption that there was no fourth gland, a third operation was performed by Dr. Churchill in March 1936, twenty-nine months after the first operation and ten years at least after the onset of the illness. The remainder of the right upper parathyroid gland was apparently of the same size as at the time of the second operation. It was resected, an amount of tissue being left in place that was about equivalent to that in a good-sized normal parathyroid gland, measuring 0.6 by 0.3 by 0.9 cm. (fig. 1). Starting two weeks after this operation, the serum calcium value gradually dropped almost to normal (fig. 1). The histologic appearance of the tissue removed was exactly similar to that of the tissue removed at the first two operations (fig. 2). This indicated that the underlying pathologic condition had persisted and also that irradiation in the doses given had had no effect on the tissue. The tissue removed at the third operation weighed only 170 mg. Therefore the estimated value of 500 mg. for the tissue left after the second operation, though the same estimation was made at both the second and the third operation, was considerably too high.

In the accompanying table the calcium and phosphorus values obtained when the patient was receiving a neutral ash, low calcium diet at various stages in the course of the illness are recorded. The calcium values are also recorded graphically in figure 1.

During the two and a half years following the first operation the patient was kept on a fairly low calcium diet to avoid if possible the development of further renal stones. During this period there gradually developed slight roentgenographic evidence of osseous disease but no symptoms thereof. The renal condition remained essentially unchanged. The patient has continued to have slow auricular fibrillation.

CASE 16^{3a}—For the more complete early history reference should be made to the first report¹. Hyperparathyroidism was discovered in October 1933, when the patient entered the hospital at the age of 26 because of renal colic. There was no

8 Albright, F., Aub, J. C., and Bauer, W. Hyperparathyroidism. A Common and Polymorphic Condition as Illustrated by Seventeen Proved Cases from One Clinic, *J. A. M. A.* **102** 1276 (April 21) 1934.

evidence of osseous disease, the serum phosphatase level was normal and there was no impairment of renal function. If one judges from the duration of the polyuria, the condition had been present for one year or slightly longer.

The preoperative serum calcium and phosphorus values, together with later values, are shown in figure 3. Dr Churchill performed the first operation on Feb. 16, 1934, and removed from the right side of the neck two enlarged glands,

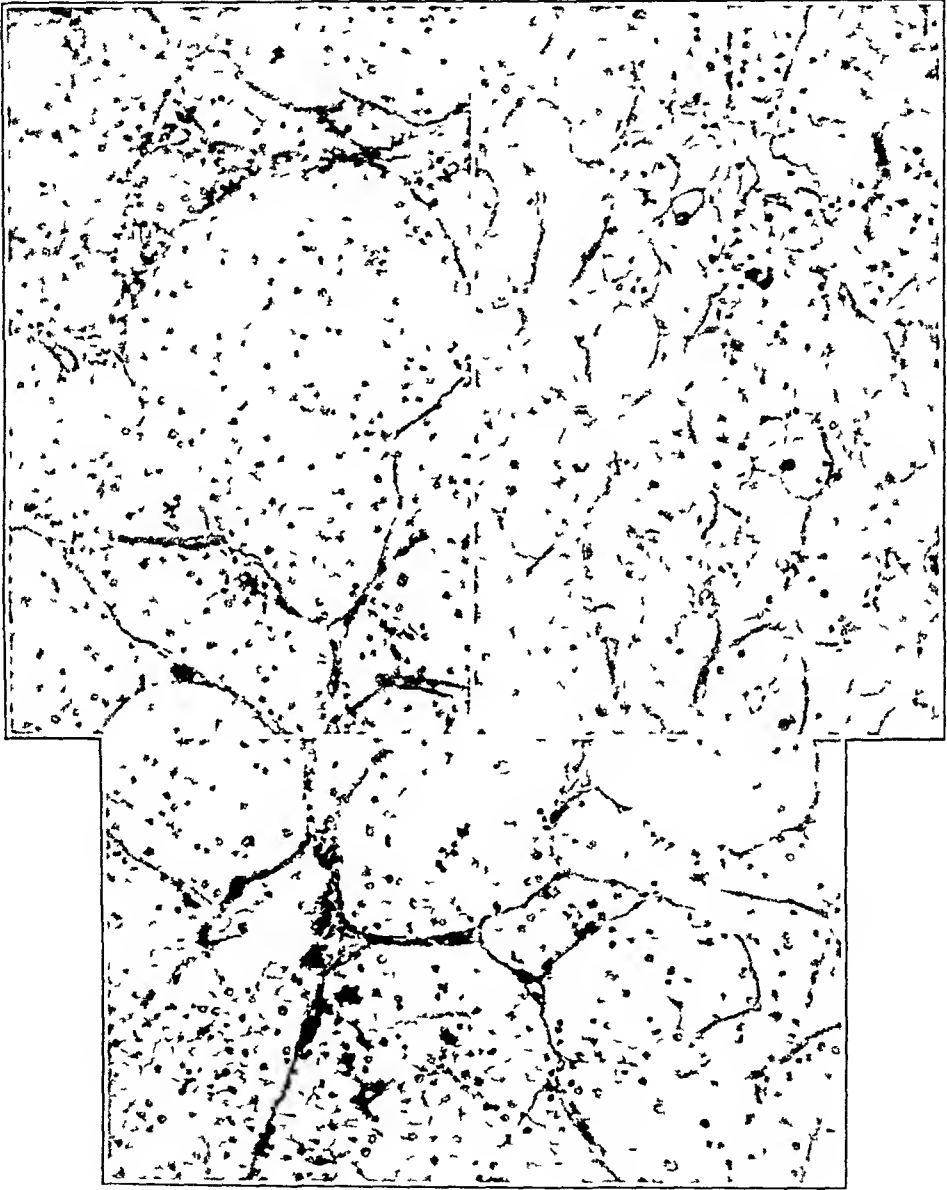


Fig. 2 (case 15) —Photomicrograph of parathyroid tissue removed at three operations, twenty-nine months having elapsed between the first and the third operation. Note that all three specimens are similar.

measuring 4.5 by 3.5 by 2.5 cm and 1.5 by 1.0 by 0.6 cm, respectively, and together weighing 15,600 mg. The other side of the neck was not explored. This was before the true nature of the disease was appreciated and before it was realized that two additional enlarged glands were to be expected on the other side. The histologic sections showed hyperparathyroidism with so-called diffuse hyperplasia. In spite of the incompleteness of the operation the serum calcium value imme-

diately fell to normal, and the urinary calcium and phosphorus values immediately dropped (fig 3) The metabolic changes will be discussed in another paper

Fifteen months after the operation the serum calcium level was still normal However, twenty-six months after operation it was clear that hyperparathyroidism was again present (fig 3) In June 1936 Dr Oliver Cope explored the other side of the neck and found, as expected, two enlarged glands The upper gland,

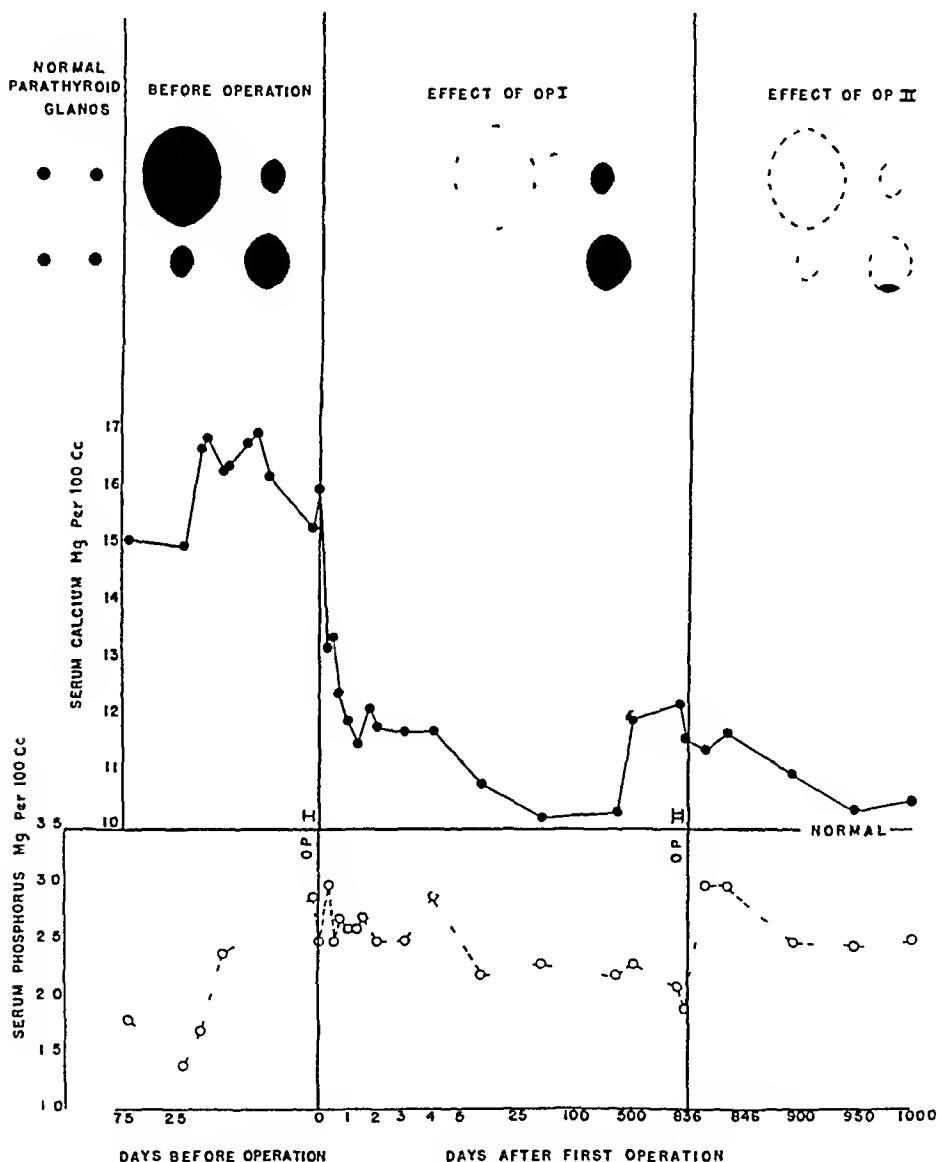


Fig 3 (case 16) —Diagram showing the serum calcium and inorganic phosphorus levels in relation to two operations on the parathyroid glands

measuring 11 by 08 by 04 cm and weighing 455 mg, was excised in toto The lower gland was resected, a piece estimated as weighing 125 mg being left behind The part removed measured 15 by 10 by 08 cm and weighed 3,350 mg The histologic picture was exactly the same as that of the tissue removed at the first operation After this procedure the serum calcium value slowly returned to normal (fig 3)

CASE 17²⁷—A more complete history was given in a previous publication¹ The diagnosis of hyperparathyroidism was made in December 1933, when the patient, a married woman of 55, entered the hospital with a fourteen months' history of renal lithiasis The menopause occurred six years before her admission to the hospital There was no skeletal involvement or renal impairment

In figure 4 the preoperative serum calcium and phosphorus values are shown, together with subsequent values On Feb 14, 1934, Dr Churchill explored the

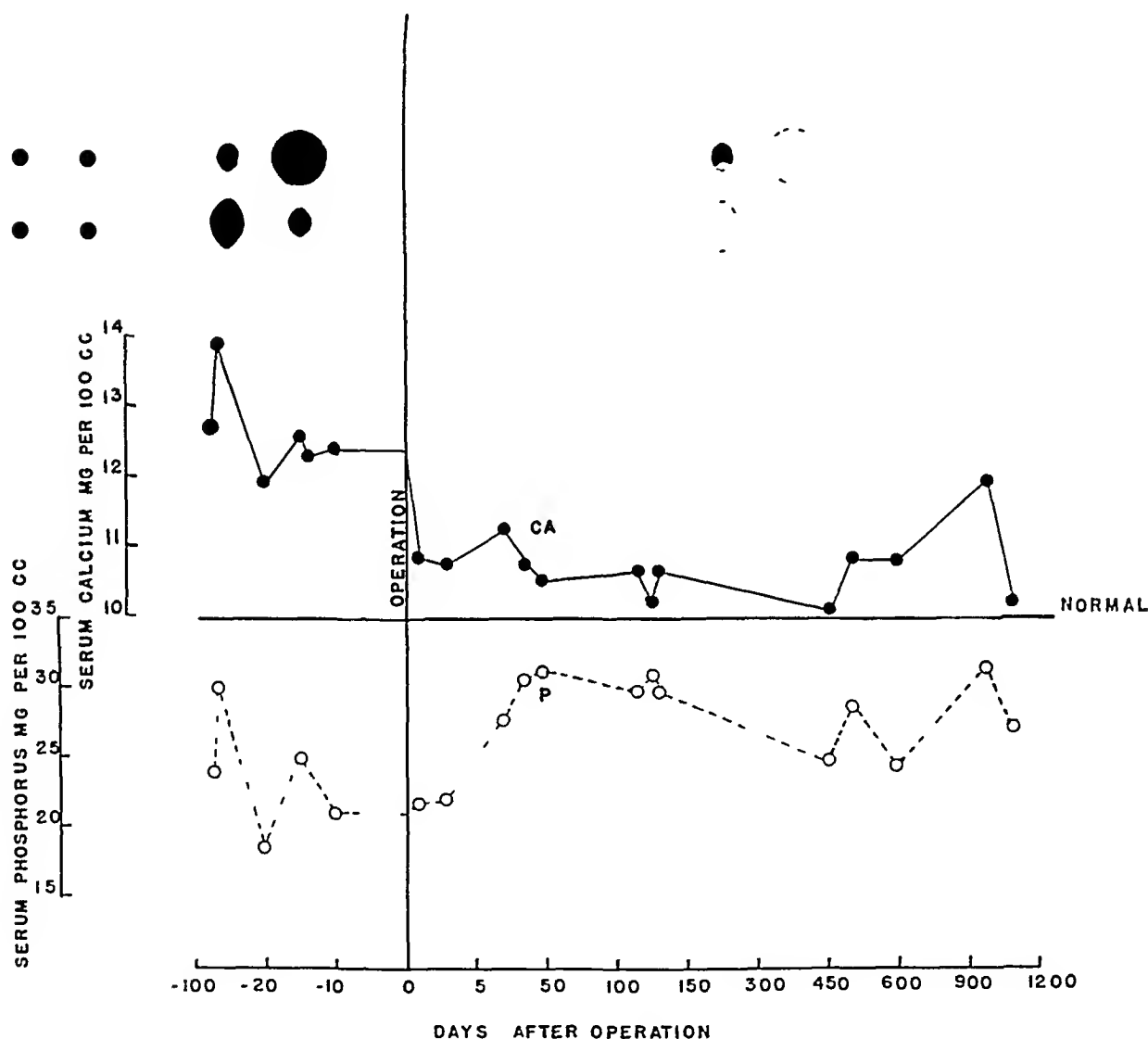


Fig 4 (case 17)—Diagram showing the serum calcium and inorganic phosphorus levels in relation to an operation on the parathyroid glands At the top of the diagram the parathyroid glands before and after operation are schematically indicated and compared with four normal parathyroid glands at the extreme left

parathyroid region and found four hyperplastic glands Three of these were removed, and a specimen was taken from the fourth gland for biopsy The respective weights and dimensions of the removed glands were left upper, 2,000 mg and 2.0 by 2.0 by 1.0 cm, left lower 600 mg and 1.0 by 0.8 by 0.4 cm, right lower, 800 mg and 1.8 by 1.2 by 0.4 cm The right upper gland, which was

left in place, unfortunately was not measured but was about the size of either of the two lower parathyroid glands. Roughly, about 500 mg of tissue was left behind. After the operation the serum calcium level immediately fell to normal (fig 4). The values were still satisfactory three years later.

CASE 23⁹—For the detailed history, reference should be made to previous publications¹⁰. This patient, a married man aged 41, a telephone lineman, entered the hospital in February 1934. His symptoms at that time were due to what proved

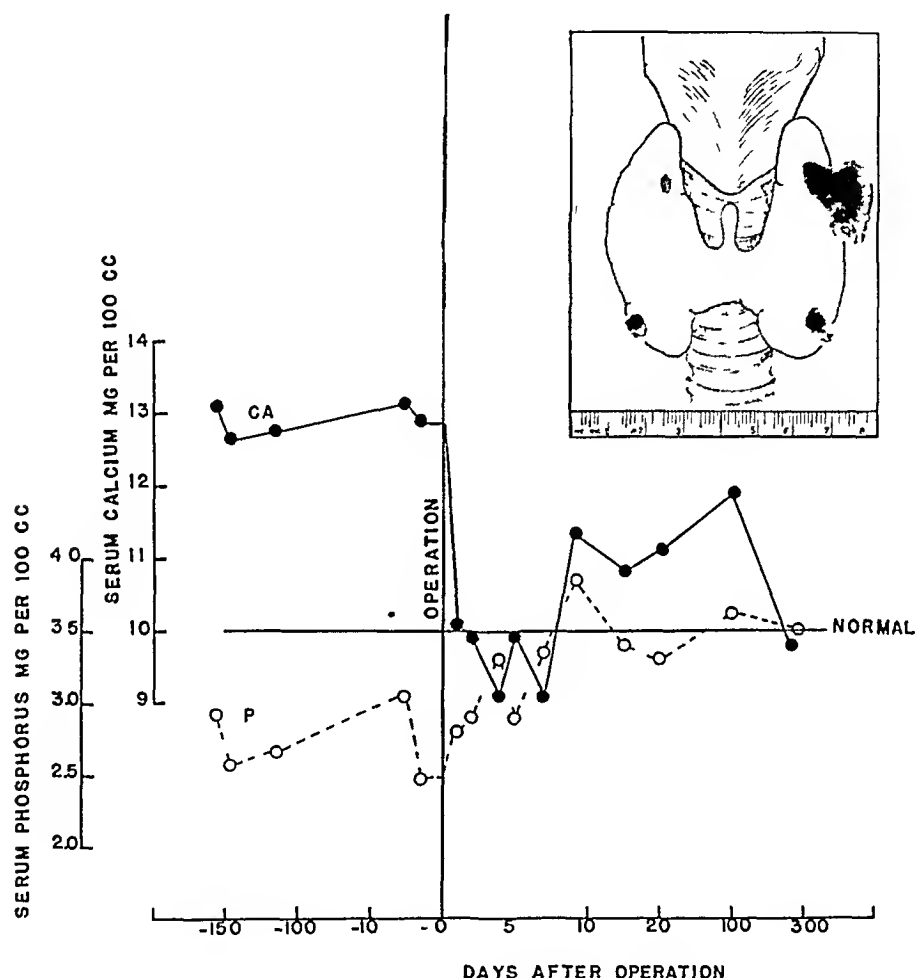


Fig 5 (case 23) —Diagram showing the effect of an operation on the serum calcium and inorganic phosphorus levels. The insert shows the three glands that were removed photographed with a conventionalized drawing as a background. The scale is in centimeters. The right upper parathyroid gland was not removed, and its size is indicated by an elliptic black area.

9 (a) Churchill, E D, and Cope, O. The Surgical Treatment of Hyperparathyroidism, Based on Thirty Cases Confirmed by Operation, *Ann Surg* **104** 9, 1936. (b) Albright, Aub and Bauer⁸. (c) Castleman, B, and Mallory, T B. Pathology of the Parathyroid Glands in Hyperparathyroidism, *Am J Path* **11** 1, 1935. (d) Albright, F. Hyperparathyroidism. A Case with Several Unusual Features, Including a Probably Non-Related Chondrosarcoma, Bence-Jones Proteinuria, and Hyperplasia of All Parathyroid Tissue, *M Clin North America* **18** 1109, 1935.

¹⁰ Churchill and Cope^{9a} Albright^{9d}

to be chondrosarcoma of the left ilium. It is doubtful that this was in any way related to the hyperparathyroidism. Six months previously he had had renal colic on the left side, and some stones had been removed from the bladder.

Roentgen examination showed prostatic calculi. Renal function tests gave excellent results. The roentgenograms of the bones, aside from those of the left ilium, were not remarkable, the serum phosphatase level was only slightly elevated. Although the diagnosis of hyperparathyroidism was made at the time of his first admission to the hospital, the chondrosarcoma was removed at that time, and it was not until July 12 that Dr. Churchill explored the parathyroid region.

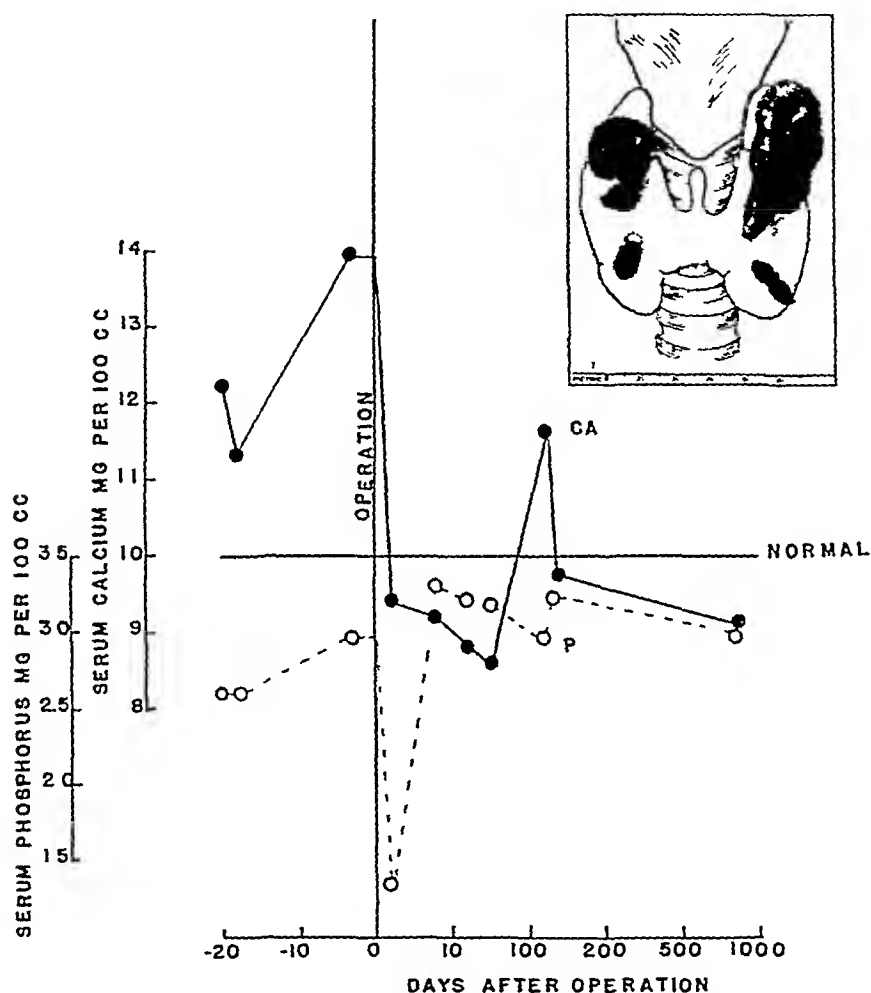


Fig 6 (case 25) —Diagram showing the effect of an operation on the serum calcium and inorganic phosphorus levels. The insert shows a photograph of the parathyroid tissue removed. The area enclosed by a dotted line indicates the amount of the right lower parathyroid gland left in place.

The preoperative serum calcium and phosphorus values are shown in figure 5, together with subsequent values. At operation all four parathyroid glands showed so-called hyperplasia. The right upper one was not enlarged, measuring 0.7 by 0.4 cm. It was not disturbed, except that a small specimen was removed for biopsy. The three remaining glands were removed. They had the following measurements and weights: right lower, 130 mg and 0.8 by 0.6 by 0.3 cm; left upper, 2,180 mg and 3.0 by 1.7 by 0.8 cm; left lower, 160 mg and 1.1 by 0.6 by 0.3 cm. The blood values returned promptly to normal and have remained satisfactory ever since (fig 5).

CASE 25¹¹—For the more complete history, reference should be made to a previous report^{9a} The patient entered the hospital in October 1934, at the age of 39 There was a four months' history of renal colic on the right side Roentgenologic examination revealed a stone in the right ureter and no evidence of osseous disease The serum phosphatase level was normal Renal function tests showed normal excretion The stone was removed

The first serum calcium and phosphorus values are shown in figure 6, together with later values Dr Cope explored the parathyroid region on October 27 and

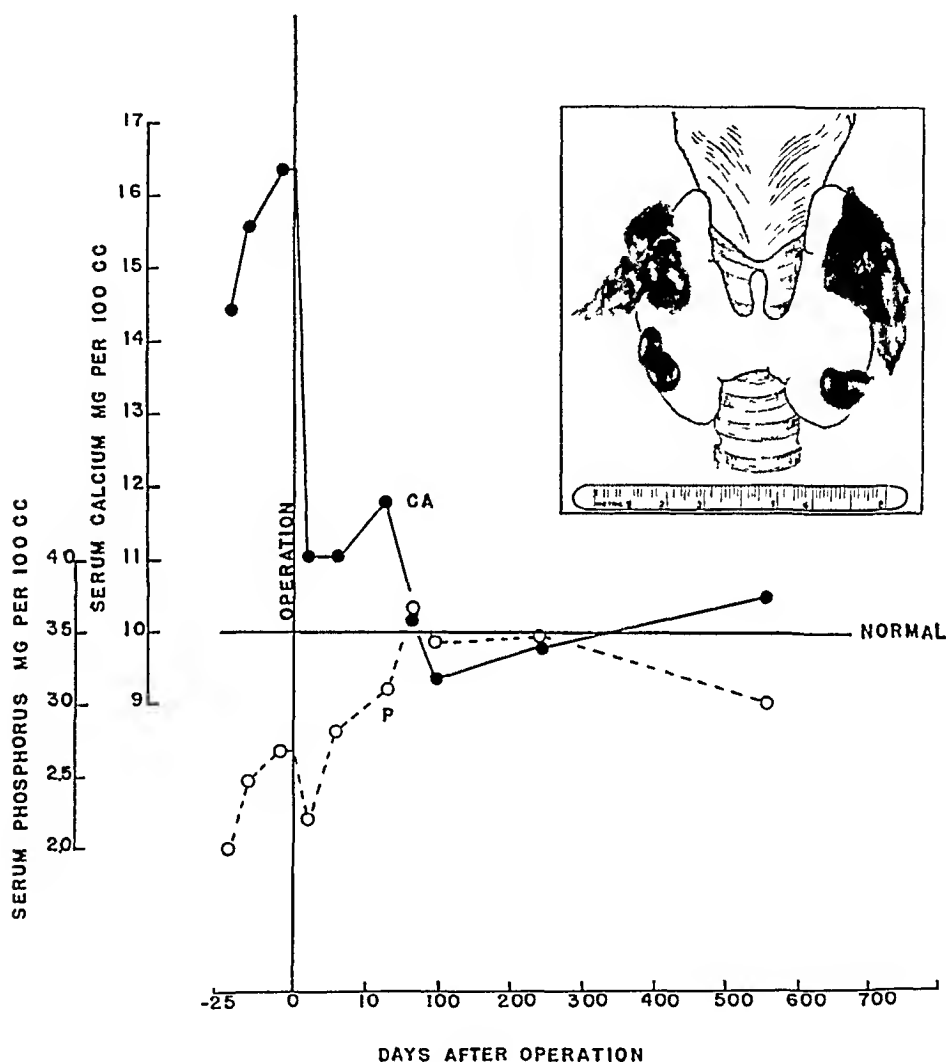


Fig 7 (case 26) —Diagram showing the effect of operation on the serum calcium and inorganic phosphorus levels The insert shows a photograph of the parathyroid tissue removed The area enclosed by a dotted line represents the tissue left in place

11 Albright, F, Sulkowitch, H W, and Bloomberg, E Further Experience in the Diagnosis of Hyperparathyroidism, Including a Discussion of Cases with a Minimal Degree of Hyperparathyroidism, *Am J M Sc* **193** 800, 1937 Churchill and Cope^{9a} Castleman and Mallory^{9c}

found all four parathyroid glands enormously enlarged. He removed all the parathyroid tissue except a piece of the lower right gland. This piece measured 0.7 by 0.4 by 0.35 cm and was estimated to weigh 40 mg. The weights of the removed glands were: left upper, 4,960 mg; right upper, 1,630 mg; left lower, 110 mg; right lower (subtotal), 100 mg. After the operation the serum calcium value returned to normal and has remained satisfactory ever since (fig. 6).

CASE 26—For a more complete history, reference should be made to a previous report^{9a}. The patient, a housewife aged 57, was admitted in January 1935. The right kidney was removed elsewhere, in 1931, because of nephrolithiasis. During the six months prior to the present admission to the hospital she had vague aches and pains throughout the skeleton. Roentgenographic studies showed generalized decalcification, indicating the diagnosis. Biopsy of bone showed osteitis fibrosa. Renal function tests showed normal functioning of the remaining kidney.

The preoperative serum calcium and phosphorus values are shown in figure 7, together with later values. In spite of definite skeletal involvement, the serum phosphatase value was not elevated. On February 9 Dr. Cope explored the parathyroid region and found four enormously enlarged glands. He removed all except a piece of the left inferior gland, estimated to weigh 225 mg. The weights of the glands removed were as follows: left upper, 6,000 mg; right upper, 3,750 mg; left lower (subtotal), 860 mg; and right lower, 590 mg. The combined weight was 11,200 mg. The serum calcium level returned to normal, where it has remained, the patient has improved markedly in weight and strength, and the skeletal pains have disappeared.

COMMENT

A Nature of the Pathologic Condition of the Parathyroid Tissue—The question has not been definitely settled whether the enlargement of the glands in this disease is due to hyperplasia and hypertrophy or just to hypertrophy of the cells. The weight of the actual mass of tissue in our six cases ranged from 19,100 to 2,510 mg, roughly one hundred to thirty times normal. Gilmour and Martin¹² found that the mean and standard deviations for the weight of parathyroid tissue are 117.6 ± 4 mg and 45.97 mg, respectively, for men and 131.3 ± 5.8 mg and 45.02 mg for women. The diameters of the individual cells are approximately three to four times normal size. Castleman and Mallory^{9c} gave as the diameter of the normal chief cell 6 to 8 microns and as the diameter of the cells in question 10 to 40 microns. Since the volume of a sphere increases as the cube of the radius, a fourfold increase in the radius would cause the volume to increase by sixty-four times. Thus, a large part, if not all, of the increase in size can be explained by hypertrophy of the cells. Further evidence that hyperplasia may be playing a subordinate role is the fact that the histologic appearance is entirely different from that seen in conditions of known hyperplasia, e. g., rickets^{12a} and renal insufficiency.²

12 Gilmour, J. R., and Martin, W. J. The Weight of the Parathyroid Glands, *J. Path. & Bact.* **44**: 431, 1937.

12a Albright, F., Butler, A. M., and Bloomberg, E. Rickets Resistant to Vitamin D Therapy, *Am. J. Dis. Child.* **54**: 529 (Sept.) 1937.

This hypothesis should be subject to proof by careful measurement of cell diameters. The problem is complicated by the fact that there is considerable variation in the size of cells (possibly due to fixing) in different sections of the same specimen. The subject is under investigation by Dr. Castleman.

One receives the impression from studying sections of tissue from these six patients that the parathyroid disturbance is an "all or none" disturbance, in that there is either a maximum degree of disturbance or none. Thus, the cells in case 23, in which there was the smallest mass of tissue, were not noticeably smaller than those in cases 16 and 26, in which there were the largest masses. No mild degree of the disease, with only slight enlargement of the cells, has been encountered. It has not been disproved as yet that the difference between case 23, in which there was 2,510 mg. of tissue, and case 26, in which there was 11,425 mg. of tissue, may not have been due to the amount of tissue which the patients had before the disease started.

Such a conception fits in with the fact that all three operations in case 15 (fig. 2) showed the same histologic changes in the parathyroid tissue and that the piece left in at the second operation apparently was just the same when seen again twenty-five months later, at the third operation. The initial cure in case 16 after the first operation, followed by a later relapse, however, suggests that the two remaining glands had increased in size between the first and the second operation. However, it is perhaps significant that this was the only one of the six cases in which at any time there was shown a tendency for the condition to grow worse as regards the degree of hyperparathyroidism, and in this case the facts are not conclusive.

The data in case 15 make it clear that the condition once it is established remains indefinitely. Thus the history shows that the condition was present in 1926, it was still present at the third operation, in 1936. Therefore it is fair to assume that the underlying abnormality was chronic. This, as previously discussed, is an important point with regard to a decision as to how much tissue to remove at operation, because once the patient has had the parathyroid glands resected to a point desirable for the so-called hyperplastic state, it would be most unfortunate to have the state correct itself.

In figure 8 the serum calcium values have been charted against the weights of parathyroid tissue at the various stages in the treatment in these six cases. The pathologic picture of the tissue being absolutely uniform, one would expect a definite correlation between the amount of tissue and the amount of serum calcium. Such was the case, especially if one believes that the two values recorded in case 15 which were not in line deviated because of a fourth parathyroid gland, which was not found. No such correlation occurs in cases of parathyroid adenoma.

The foregoing observations suggest that the condition under discussion has not yet been proved to be neoplasia or hyperplasia but may be a disorder of function. It seems possible, for example, that under normal conditions the parathyroid hormone is made and released according to the needs of the body, the stimulus perhaps being a tendency for the serum calcium content to fall below 10 mg per hundred cubic centimeters. In the condition under discussion there may be a disturbance in the production of parathyroid hormone by the cells, the production being tremendously speeded up. The release mechanism

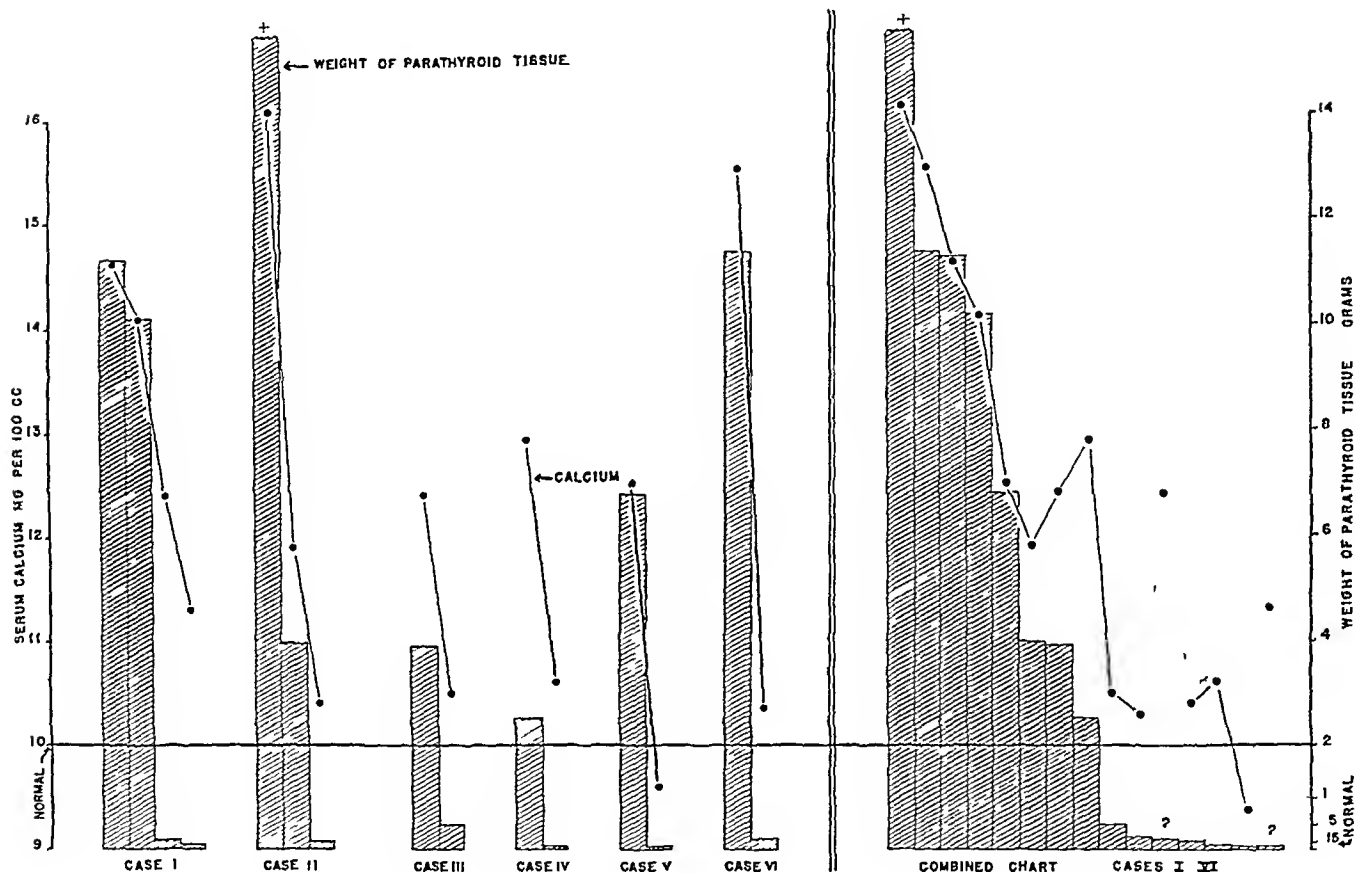


Fig 8—Diagram showing the correlation between the weight of the parathyroid tissue at the various stages in the treatment of the six patients and the level of the serum calcium. Question marks and dotted lines indicate points where there may be a marked error in the diagram because the fourth gland was never found in case 15. Cases I to VI, inclusive, in the diagram correspond to cases 15, 16, 17, 23, 25 and 26, respectively, described in the text.

may still attempt, with only partial success, to hold the hormone back as much as possible, and the swelling of the glands may be due to the fact that the cells are distended with hormone. It would be helpful if one knew whether such tissue contains more hormone per unit of weight than other parathyroid tissue. It would also be interesting to know whether the swollen aspect of the cells disappears when the amount

of tissue has been reduced sufficiently so that the serum calcium value is on the low side (case 26). These wholly theoretic observations are included here in the hope that the next person encountering such a patient will save some tissue for biologic assay¹³

Case 23 is of interest in that one gland, although histologically similar to the others, was no larger than a normal gland—weighing about 40 mg. The largest gland in this case weighed 2,180 mg. If one assumes that this gland weighed one-fortieth as much, or 54.5 mg., before the disease occurred, then the small gland must have weighed 1 mg. This probably explains why normally one often can find only three glands, although embryologic studies have shown that four glands are almost sure to be present¹⁴

B Treatment of the Disease—Regardless of what the exact nature of the disease is, it can now be said with a fair degree of assurance that the condition is amenable to surgical treatment. As previously discussed, the underlying pathologic condition is persistent (for at least ten years in case 15), and if the surgeon removes all the tissue except about 200 mg., it appears from the data assembled that there should be a permanent cure. In all the cases here considered the patient has been followed for over two years postoperatively, and one patient (case 17) who had about 400 mg. of tissue left in place is still in an isoparathyroid state, over three years after operation.

It should be noted that if one leaves out of consideration case 15, in which the possibility of a fourth gland is not unlikely, the removal of all but 400 mg. or less of parathyroid tissue was attended by cure. There are no data for remnants weighing between 400 and 2,510 mg. (before operation in case 23). Therefore, one cannot say that the leaving of 1,000 mg., for example, might not be attended by permanent cure. This is an important question, as the more that can be left in without causing recurrence, the safer the operation will be and the less a subsidence of the so-called hyperplastic state is to be feared. It should be remembered, of course, that the amount of parathyroid tissue which must be left in place is increased if renal insufficiency¹⁵ or marked osseous disease is present.¹⁶

C Cause of the Pathologic State of the Parathyroid Glands—The cause of the pathologic condition remains completely obscure. In the previous paper considerable circumstantial evidence was presented suggesting that the condition may be secondary to an excess of pituitary

13 Dr. Collip has informed us that the tissue should be preserved in ten parts of acetone for this procedure.

14 Norris, E. H. *The Parathyroid Glands and the Lateral Thyroid in Man. Their Morphogenesis, Histogenesis, Topographic Anatomy and Prenatal Growth*, Publication 479, Carnegie Institution of Washington, 1937, p. 247.

15 Albright, Drake and Sulkowitch.² Churchill and Cope.¹⁷

parathyrotropic substance. No confirmatory evidence has been obtained. It should be noted that the changes in rabbit parathyroid glands described by Hertz and Kranes as the result of injections of pituitary substance were of the nature of true hyperplasia, with mitotic figures. Mitoses have not been noted in any of the parathyroid tissue in the disease under consideration.

Roentgenographic examinations of the skulls in all six cases failed to demonstrate any evidence of a pathologic condition of the pituitary body. Roentgen radiation of the pituitary body was without benefit in case 15. Massive treatment with estrogenic substance (which depresses the pituitary hormone in many cases) had no effect in case 15. Whereas two of the patients (cases 15 and 17) had passed the menopause and had the expected increase of follicle-stimulating hormone in the urine, no such increase was found in cases 16, 23 and 25. In cases 15 and 26 the sugar curves were definitely typical of diabetes, but there was no suggestion of diabetes in the other cases, and the sugar curve was perfectly normal in case 16.

SUMMARY AND CONCLUSIONS

Six cases of hyperparathyroidism with what has previously been termed primary hyperplasia of the parathyroid glands are reviewed.

It is pointed out that the pathologic condition of the parathyroid glands is histologically dissimilar from that in cases of undoubted hyperplasia of parathyroid tissue, that it has not yet been shown that the enormous enlargement of the glands in this condition (about thirty to one hundred times) cannot be explained by hypertrophy of the cells and that the condition may be a disorder of hormone production rather than hyperplasia.

The studies showed that all the glands from all six patients on all occasions revealed a similar histologic picture, it is suggested that the tissue change is an "all or none" one.

A distinct correlation was observed between the weight of the parathyroid tissue and the degree of hyperparathyroidism, this was in marked contrast to the situation in cases of parathyroid adenoma.

Evidence is presented that the underlying cause of the changes in the parathyroid glands is a chronic one (in one case the condition had existed for at least ten years).

There was little, if any, evidence of a tendency for the parathyroid tissue left in place after partial resection to regenerate, so the condition is apparently amenable to permanent surgical cure. The optimum amount of tissue to be left in place at operation has not yet been determined, but anything less than 400 mg is probably not too much.

No evidence has been obtained to confirm the hypothesis that the condition is secondary to overactivity of some pituitary hormone.

REMOVAL OF INTRAVENOUSLY INJECTED BROM-SULPHALEIN FROM THE BLOOD STREAM OF THE DOG

A COMPARISON OF THE REMOVAL OF INTRAVENOUSLY INJECTED
BILIRUBIN AND THAT OF BROMSULPHALEIN

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AND

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We¹ have previously reported observations on the effect of various experimental procedures on the removal of intravenously injected bilirubin from the blood stream of the dog. These observations may be briefly summarized as follows. The normal rate of removal is extremely rapid when compared with that in man, it is characterized by a prompt disappearance of 50 to 60 per cent of the amount injected within the first five minutes and a subsequent progressive decline in the plasma levels so that bilirubin is no longer detectable in the plasma after sixty to ninety minutes with a 5 mg. per kilogram dose and after ninety to one hundred and twenty minutes with a 10 mg. per kilogram dose, anesthesia produces a definite impairment in the rate of removal, obstruction of the bile ducts results in an immediate complete impairment of removal, reticuloendothelial blockade produces a slight but definite impairment, and the intravenous administration of decholin sodium has only minor and perhaps negligible effects. The removal of intravenously injected dyes such as bromsulphalein from the blood stream has been used as a method of studying hepatic function. However, there are suggestions in the literature that the removal of bromsulphalein from the blood stream might not be affected by some of the aforementioned procedures to the same degree as the removal of bilirubin. For example, various workers, including ourselves, have found that reticuloendothelial blockade produces a marked impairment in the removal of bromsulphalein from the blood stream.² Also it is indicated by the work of Snell,

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1 Dragstedt, C. A., and Mills, M. A. *Am. J. Physiol.* **119** 713, 1937

2 (a) Herlitz, C. *Acta pædiat. (supp. 5)* **12** 1, 1931. (b) Klein, R., and Levinson, S. A. *Proc. Soc. Exper. Biol. & Med.* **31** 179, 1933. (c) Mills, M. A., and Dragstedt, C. A. *ibid.* **34** 228, 1936

Greene and Rowntree³ and others that obstruction of the bile ducts is not followed by immediate impairment of dye removal, as is the case with bilirubin. The present study was therefore designed to determine the effects of various experimental procedures on the rate of removal of bromsulphalein so that a comparison with the observations on bilirubin could be made, in the hope that the data would aid in the understanding of the interrelations between the Kupffer cells and the parenchymal cells of the liver and thus in the interpretation of various tests of hepatic function.

METHODS

The dose of bromsulphalein employed in the tests was 2 mg per kilogram of body weight injected intravenously. Samples of blood (oxalated) were drawn five and thirty minutes after the injection. The plasma was alkalinized by the addition of 2 drops of tenth-normal sodium hydroxide, and readings were made in a comparator box against freshly prepared standards. As is customary with this technic, the reported values represent the percentage of dye present in the plasma and are computed on the assumption that the volume of blood is 10 per cent of the body weight.

In the course of our studies of the plasma levels of bilirubin and bromsulphalein after intravenous injection there have been definite indications that the rates of decline of values for these substances have a biphasic character. The first, or primary, phase may be described as that obtaining during the first five minutes (roughly) and the second, or secondary, phase as that subsequent to this five minute interval. The evidence presented in this paper indicates that various procedures may primarily affect one or the other phase, so that it seems of some advantage to use these terms descriptively in relating our observations.

RESULTS

1 *Removal of Bromsulphalein in Unanesthetized Dogs*—The data for 18 normal dogs are shown in table 1. The values agree in general with those obtained by others. Bromsulphalein disappears from the blood with great rapidity, 85 to 95 per cent is removed within five minutes and the remainder within thirty minutes. The rate of removal is thus greater than that of bilirubin, 50 to 60 per cent of which disappears within five minutes, sixty to ninety minutes being required for complete removal of the remainder. This ratio holds true when amounts of bromsulphalein up to 5 mg per kilogram are employed. Thus the major part of the injected bromsulphalein leaves the blood stream during the primary phase, while approximately equal amounts of bilirubin are removed during the primary and the secondary phase.

2 *Removal of Bromsulphalein in Dogs During Anesthesia*—The data for 29 animals are shown in table 1. Surgical anesthesia with ether or ether and barbital of from one to two hours' duration has no

3 Snell, A. M., Greene, C. H., and Rowntree, L. G. Diseases of the Liver. Comparative Study of Certain Tests for Hepatic Function in Experimental Obstructive Jaundice, *Arch Int Med* 36:273 (Aug.) 1925.

appreciable effect on the rate of removal of bromsulphalein from the blood stream. Comparable degrees of anesthesia materially impair the removal of bilirubin. Chloroform anesthesia or deep or prolonged anesthesia with ether and barbitol affects the rate of removal of bromsulphalein (see also the article by Rosenthal and Bourne⁴).

3 Removal of Bromsulphalein in Dogs After Ligation of the Bile Ducts—The data for 7 animals after various types of ligation and after various intervals are shown in table 1. Even after ligation of both the common and the cystic duct there is no appreciable reduction in the rate of removal of bromsulphalein for periods up to three hours. Our results agree in general with those of Snell, Greene and Rowntree,³ who employed phenoltetrachlorophthalein after various types of ligation in dogs and reported that no retention of dye occurred for a number

TABLE 1—Rate of Removal of Intravenously Injected Bromsulphalein from the Blood Stream

Procedure	Number of Dogs	Bromsulphalein, Mg per Kg	Bromsulphalein, %		Conditions
			5 Min	30 Min	
Normal animals	3	2	5	0	Normal
	10	2	10	0	Normal
	3	2	15	0	Normal
	2	5	15	0	Normal
Anesthesia	3	2	10	0	Ether
	12	2	5-15	0	Ether barbitol
	4	2	10	0	Avertin
	5	2	15-50	0-15	Chloroform
Reticuloendothelial blockade	14	2	30-80	10-50	Complete data given previously ^{2c}
Ligation of ducts	2	2	5-20	0	Common duct, 1 hr
	2	2	15-35	0-20	Common duct, 24 hr
	1	2	10	0	Common and cystic ducts, 1 hr
	1	2	15	10	Common and cystic ducts, 3 hr
	1	2	10	10	Common and cystic ducts, 4 hr
Decholin	2	5	45-50	10-15	5 cc decholin 5 min before test
	2	2	40-60	0-5	2-5 cc decholin 5 min before test

of hours or until bilirubinemia resulting from the obstruction was present. Our findings obtained with bromsulphalein are in striking contrast to those obtained with bilirubin. Even if the bilirubin is injected as soon after ligation of the ducts as is practicable, the secondary phase of removal of bilirubin is completely inhibited.

4 Removal of Bromsulphalein in Dogs After Reticuloendothelial Blockade—We^{2c} have previously confirmed the report of Klein and Levinson^{2b} that reticuloendothelial blockade produced by the intravenous injection of india ink produces a marked retention of subsequently injected bromsulphalein. The daily injection of 20 cc of 8 per cent india ink in saline solution for from three to eight days results in

⁴ Rosenthal, S. M., and Bourne, W. Effects of Anesthetics on Hepatic Function, J. A. M. A. 90:377 (Feb. 4) 1928.

retention of from 30 to 80 per cent of the dye during the primary stage and from 10 to 50 per cent during the secondary phase. Similar degrees of blockade result in some impairment of the removal of injected bilirubin. Not only is the retention of bilirubin less striking than that of bromsulphalein, but it occurs almost entirely in the secondary phase of the bilirubin curve.

5 *Removal of Bromsulphalein in Dogs Under the Influence of Decholin*—Decholin (20 per cent sodium dehydrocholate) was employed as a cholagogue, as it was thought that an increased rate of excretion of bile should have a significant effect on the rate of removal of materials excreted exclusively or mainly in the blood. Negligible effects were observed when decholin was injected previous to the administration

TABLE 2—*Summary of Data*

Condition	Bilirubin	Bromsulphalein
Normal	50 to 60% removed during primary phase, 40 to 50% during secondary phase	Rate of removal very rapid, 85 to 95% in primary phase, 5 to 15% during secondary phase
Anesthesia	Slight effect on primary phase, somewhat greater effect on secondary phase	No effect in either phase until after prolonged or deep anesthesia
Reticuloendothelial blockade	Definite impairment in secondary phase of removal, slight effect in primary phase	Marked impairment in primary phase, impairment of secondary phase
Obstruction of bile ducts (without bilirubinemia)	Immediate and complete impairment of secondary phase	No initial impairment of either phase, later impairment of secondary phase, then primary phase
Decholin	Negligible effect in primary phase, possibly some augmentation of secondary phase	Marked impairment of primary phase, slight effect on secondary phase

of bilirubin and during the ensuing two hours after the injection in the normal dog. The injection of decholin before that of bromsulphalein, however, resulted in retention of the dye. This effect was most marked during the primary phase of the curve and was usually absent in the secondary phase.

COMMENT

The available evidence indicates rather conclusively that both bromsulphalein and bilirubin when injected intravenously are ultimately almost completely excreted by the liver in the bile. Nevertheless the two substances leave the blood stream at different rates and these rates of removal from the blood stream are affected both qualitatively and quantitatively in different degrees by various procedures. The conspicuous feature of the removal of bromsulphalein from the blood stream is the abrupt fashion with which 85 to 95 per cent disappears within five minutes. It is inconceivable that this proportion of the dye is excreted so rapidly in the bile, and direct observations on the

appearance of the dye in the bile confirm this view⁵ A significant proportion (50 to 60 per cent) of the injected bilirubin likewise leaves the blood stream within five minutes, but the remaining portion (40 to 50 per cent) not only is considerably in excess of the corresponding remnant of bromsulphalein but may also be more readily associated with its excretion in the bile Anesthesia, which depresses the secretion of bile, impairs the secondary phase of removal of bilirubin more markedly than that of bromsulphalein Ligation of the bile ducts, which completely suppresses the secretion of bile, likewise impairs the removal of bilirubin more strikingly than it does in the case of bromsulphalein We⁵ have elsewhere presented evidence that such retention of dye as does occur after ligation of the ducts is subsequent to and related to the ensuing bilirubinemia

Moderate to marked retention of bromsulphalein occurred in all animals in which blockade with india ink was carried out,⁶ the degree generally varying directly with the postulated degree of blockage (as indicated by the number of daily injections of india ink) Although both the primary and the secondary phase of dye removal are affected, the more marked retention seems to occur during the former This is in contradistinction to the rate of removal of bilirubin The amount of bilirubin which is removed during the primary phase is only slightly less than that for the normal animal, and the more marked interference with removal of the pigment occurs during the secondary phase of the curve

The intravenous administration of decholin to normal or anesthetized dogs either had no effect or appeared to facilitate the removal of bilirubin to some extent Similar injections of decholin before injections of bromsulphalein, however, resulted in a striking retention of the injected dye Thus, measures which suppress the secretion of bile do not correspondingly suppress the removal of bromsulphalein from the blood stream, and a measure which increases the secretion of bile not only does not enhance the removal of the dye from the blood stream but actually interferes with it As opposed to this, measures which suppress the secretion of bile impair the removal of intravenously injected bilirubin, and, conversely, measures which increase the output of bile either facilitate the removal of the pigment from the blood stream or have no appreciable effect

5 Dragstedt, C A, and Mills, M A Proc Soc Exper Biol & Med **34** 467, 1936, Am J Physiol **119** 713, 1937

6 In speaking of reticuloendothelial blockade in connection with this article, we feel that a "blockade" produced by intravenous injections of india ink may probably be considered to be no more than a temporary and incomplete reduction of function of the littoral cells of the reticuloendothelial system (those in direct contact with the blood stream) and that there is little evidence that any other cells of the system are more than slightly affected (Mills, M A To be published)

CONCLUSION

It is thus clear that, used as a test of hepatic function, the rate of removal of intravenously injected bromsulphalein from the blood stream when abnormal does not indicate the same pathologic condition as would corresponding alterations in the test with bilirubin. The evidence is largely circumstantial, but it seems fairly well indicated that the removal of bromsulphalein from the blood stream is brought about chiefly by the activity of the reticuloendothelial system (of which the Kupffer cells in the liver constitute an important fraction) and that, correspondingly, disturbances in the removal of dye reflect some impairment of function in this system of cells. Aside from the initial fractional removal of bilirubin (which can probably be accounted for by diffusion into the tissue, engulfment by the reticuloendothelial system, etc.), the removal of bilirubin from the blood stream seems to be dependent on and related to its excretion in the bile, and, correspondingly, disturbances in the removal of bilirubin reflect some impairment in this function, which is presumably related to the parenchymal cells of the liver.

EXCRETION OF BILE PIGMENT AND HEPATIC FUNCTION IN DISEASES OF THE BLOOD

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The excretion of an abnormally large amount of bile pigment has long been recognized as an almost constant feature of pernicious anemia in relapse. Furthermore, the excretion of bile pigment has been found to return to normal after the institution of adequate treatment¹. The significance of these observations has given rise to considerable controversy. One school of thought² holds the view that the bile pigment formed in the normal course of destruction of blood or possibly through some activity of the liver apart from that of the destruction of blood cannot be utilized for the formation of new blood in patients with pernicious anemia and hence is excreted almost quantitatively. The second school³ regards the increased excretion of bile pigment in pernicious anemia as evidence of excessive destruction of red blood cells. In this study the metabolism of bile pigment in various forms of blood dyscrasia has been investigated, and the results in pernicious anemia have been compared with those obtained in other forms of anemia.

The quantitative determination of the urobilinogen excreted in the feces is generally accepted as the most reliable method of studying the excretion of bile pigment in human beings. Jaundice, an elevated serum

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1 (a) Watson, C J. The Average Daily Elimination of Urobilinogen in Health and in Disease, with Special Reference to Pernicious Anemia, *Arch Int Med* **47** 698-726 (May) 1931. (b) Farquharson, R F, Borsook, H, and Goulding, A M. Pigment Metabolism and Destruction of Blood in Addison's (Pernicious) Anemia, *ibid* **48** 1156-1185 (Dec) 1931. (c) Filo, E. Die Wirkung der Leberbehandlung auf die Bildung und Ausscheidung der Gallenfarbstoffe bei perniziöser Anämie, *Folia haemat* **44** 368-384, 1931.

2 Whipple, G H. Pigment Metabolism and Regeneration of Hemoglobin in the Body, *Arch Int Med* **29** 711-731 (June) 1922, Hemoglobin Construction Within the Body as Influenced by Diet Factors. Consideration of Anemia Problems, *Am J M Sc* **175** 721-733, 1928. Castle, W B, and Minot, G R. *Pathological Physiology and Clinical Description of the Anemias*, New York, Oxford University Press, 1936, p 10.

3 Krumbhaar, E G. Thoughts on the Morbid Processes Active in Pernicious Anemia, *Am J M Sc* **175** 523-527, 1928. Dock, W. The Importance of Hemolysis in the Pathogenesis of Macrocytic Anemia, in *Medical Papers Dedicated to Henry Asbury Christian*, Baltimore, Waverly Press, Inc, 1936, pp 545-558.

content of bilirubin and an increased urinary content of urobilin are all suggestive of an increase in formation and excretion of bile pigment but cannot be accepted as conclusive proof of it, since each of these three signs, alone or in any combination, may be found in the presence of hepatic disease when the total excretion of bile pigment may be normal or even subnormal. It is for that reason that in this study the average daily output of urobilinogen in the feces has been chiefly relied on as an index of the output of bile pigment. Parallel with the determinations of urobilinogen in the feces, the output of urobilinogen in the urine has been quantitated in most cases, and in order to obtain a better idea of the condition of the liver, one or more tests of hepatic function have been made in certain of the cases studied.

The two tests of hepatic function which have been employed in this study are (1) the test of bilirubin excretion and (2) the test of hippuric acid synthesis. The first, introduced by Eilbott⁴ and von Bergmann⁵ in 1927, has recently been developed by Harrop and Barron⁶ and by Soffer and Paulson⁷ in this country. Soffer⁸ has stated that he regards it as the most sensitive test of the excretory function of the liver. In 1932 Quick⁹ introduced a test for hepatic function based on the synthesis and excretion of hippuric acid after the oral administration of sodium benzoate. Since the synthesis depends on the conjugation of benzoic acid (an aromatic compound) with aminoacetic acid to form hippuric acid, Quick said he regards this test as a measure of the protective mechanism of the body. In view of the distinct possibility that a hemolytic toxin may play a role in the etiology of pernicious anemia, in addition to the fact that certain other types of blood dyscrasia appear to be produced by aromatic compounds (e g, benzene, arsphenamine and aminopyrine), it was desirable to have a test of the ability of the liver to detoxify such substances.

4 Eilbott, W. Funktionsprüfung der Leber mittels Bilirubinbelastung, *Ztschr f klin Med* **106** 529-560, 1927.

5 von Bergmann, G. Zur funktionellen Pathologie der Leber insbesondere der Alkohol-Aetiologie der Cirrhose, *Klin Wchnschr* **6** 776-780, 1927.

6 Harrop, G. A., and Barron, E. S. G. The Excretion of Intravenously Injected Bilirubin as a Test of Liver Function, *J Clin Investigation* **9** 577-587, 1931.

7 Soffer, L. J., and Paulson, M. Comparative Advantages and Further Modification of the Bilirubin Excretion Test for Hepatic Function, *Am J M Sc* **192** 535-540, 1936.

8 Soffer, L. J. Present-Day Status of Liver Function Tests, *Medicine* **14** 185-254, 1935.

9 Quick, A. J. Conjugation of Benzoic Acid with Glycine, a Test of Liver Function, *Proc Soc Exper Biol & Med* **29** 1204-1205, 1932, The Synthesis of Hippuric Acid. A New Test of Liver Function, *Am J M Sc* **185** 630-635, 1933.

METHODS

Excretion of Urobilinogen—The content of urobilinogen in the feces and in the urine was determined quantitatively by Watson's¹⁰ modification¹⁰ of Terwen's¹¹ original method. The method depends on reducing urobilin to urobilinogen with ferrous hydroxide and then combining the urobilinogen with paradimethylaminobenzaldehyde to produce a red solution which can be compared colorimetrically with a phenolphthalein standard.

Stools were collected over a three or four day period. Two different methods of collection were employed. (a) The stools were collected on waxed paper and kept in a previously weighed cardboard carton in the ice box until the end of the collection period. The carton was then weighed once more, and the total weight of the stool was thus determined. The total three or four day collection of stool was thoroughly mixed in a mortar, and a 5 Gm aliquot was taken for determination of the urobilinogen content. (b) Stools were collected in large enamel buckets, which were kept in the ice box until the end of the collection period. Sufficient water was added to make up a thick suspension, which was transferred to a 2 liter glass bottle and stirred for fifteen to thirty minutes with an air-driven stirring rod. After the suspension had been rendered homogeneous, the whole was measured, and a 5 to 20 cc aliquot was taken for the determination of urobilinogen. This second method proved more satisfactory.

Urine for the determination of urobilinogen was collected over a twenty-four to forty-eight hour period, 10 cc of a saturated alcoholic solution of salicylic acid or 2 cc of toluene serving as a preservative. The collection bottles were kept in the ice box.

The results are expressed in terms of the average twenty-four hour output of urobilinogen in milligrams. Watson¹⁰ has given the following upper limits of normal: in the feces, 250 mg for males and 175 mg for females, in the urine, 2 to 25 mg a day.

Hepatic Function Tests—(a) The bilirubin excretion test was carried out in the manner described by Harrop and Barron, in the earlier tests the colorimeter was employed, whereas more recently the potassium dichromate standards devised by Soffer and Paulson for direct comparison with the acetone-treated blood plasma have been used. The patients were given 1 mg of bilirubin per kilogram of body weight intravenously. Retention of more than 5 per cent of the injected bilirubin after four hours is regarded as evidence of hepatic dysfunction.

(b) The test of hippuric acid synthesis was carried out according to the original directions of Quick, the sodium hydroxide titration being employed in preference to the more complicated ether extraction method. Although the method actually determines the amount of hippuric acid in the urine, the results are expressed in terms of benzoic acid. Quick concluded that normal persons should excrete at least 3 Gm of benzoic acid within four hours after the ingestion of 59 Gm of sodium benzoate. Thus the excretion of less than 3 Gm of benzoic acid in four hours may be regarded as evidence of hepatic damage, provided intestinal absorption and renal function are normal.

¹⁰ Since the present study was undertaken C J Watson (Am J Clin Path 6 458, 1936) has published a further modification of the method which gives more satisfactory measurements of urobilinogen in the urine but makes little difference in determinations of this substance in the feces (Watson, C J. Personal communication to the author).

¹¹ Terwen, A J L. Ueber ein neues Verfahren zur quantitativen Urobilinbestimmung in Harn und Stuhl, Deutsches Arch f klin Med 149 72-101, 1925.

Examination of the Blood—For blood counts and hematocrit determination, 4 cc of venous blood was placed in a small rubber-stoppered glass bottle with 0.02 cc of a 20 per cent solution of potassium oxalate as an anticoagulant. Standardized pipets and counting chambers were employed for cell counts. The hemoglobin value was determined by the Sahli method, 100 per cent representing 14.5 Gm per hundred cubic centimeters of blood. Reticulocytes were counted in blood smears made on cover slips previously stained with brilliant cresyl blue and subsequently counterstained with Wright's stain. Wintrobe hematocrit tubes were employed in determining the volume of packed erythrocytes, from which the mean corpuscular volume was readily calculated. The icterus index was determined by the Meulengracht method.

The fragility of the erythrocytes was determined by the usual method, 1 drop of a 50 per cent suspension of washed red blood cells being added to 2 cc of the saline solution. Saline dilutions from 0.5 to 0.26 per cent, kept in stock bottles, were employed for routine tests, when markedly increased fragility necessitated it, fresh solutions were made up, beginning at 0.8 per cent. A control test was made with each unknown. Since the minimum resistance for controls was always at 0.46 or 0.44 per cent, hemolysis beginning at 0.48 per cent or above was regarded as signifying decreased minimum resistance (or increased fragility), hemolysis beginning at 0.42 per cent or below, as evidence of increased minimum resistance (or decreased fragility). With the control levels for maximum resistance varying from 0.36 to 0.34 per cent, complete hemolysis at 0.38 per cent or above was regarded as signifying decreased maximum resistance, complete hemolysis at 0.32 per cent or below, as evidence of increased maximum resistance.

MATERIAL

The present study included 74 patients with blood dyscrasias for whom determinations of urobilinogen were carried out. Either the bilirubin excretion test or the hippuric acid synthesis test of hepatic function or both were performed on 48 of the 74 patients. The patients were divided into five groups, according to the disorder presented, as follows: (1) pernicious anemia and sprue, (2) hemolytic anemias, (3) aplastic anemias, (4) leukemias and (5) miscellaneous conditions, which included primary hepatic disease, Banti's syndrome, polycythemia vera and Hodgkin's disease. Complete blood counts were made for all patients, and additional data, such as erythrocyte fragility, reticulocyte counts and icterus index, were obtained in many cases. The results of these studies will be discussed separately under the individual headings.

RESULTS

Group 1 Pernicious Anemia and Sprue—Fourteen patients make up this group: 10 with typical Addison's pernicious anemia, 1 with pernicious anemia of pregnancy, 1 with macrocytic anemia associated with intestinal anastomosis and 2 with tropical sprue.

The average daily excretion of urobilinogen in the feces was determined in 9 of the 10 cases of pernicious anemia during relapse, and in 8 of the 9 cases the values obtained were well above the upper limit of normal, the highest value being 1,050 mg per day in case 2. One patient (case 4) in a mild relapse gave a normal value. In the 4 cases in which determinations of the urobilinogen excretion were carried out

after adequate therapy with liver extract, the values had returned to normal levels. The observation that the amount of urobilinogen excreted in the feces is as a rule elevated during a relapse of pernicious anemia and returns to normal after liver therapy confirms the findings of numerous other workers. Two patients (cases 2 and 5), who were followed during the pretreatment and post-treatment periods, well illustrate the progressive decrease in the rate of excretion of bile pigment after treatment has been instituted (charts 1 and 2). Case 2 (chart 1)

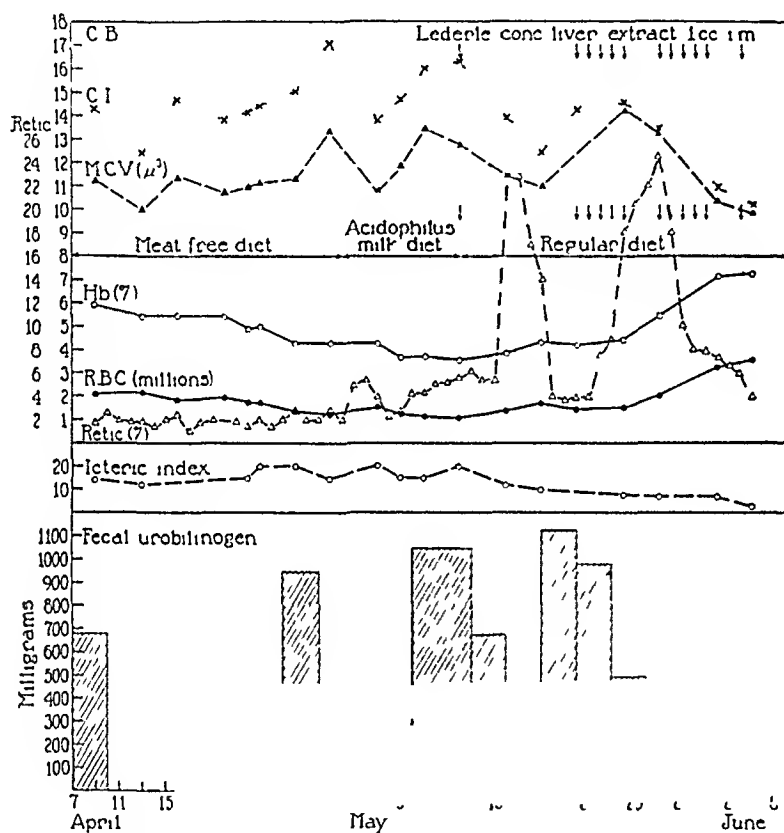


Chart 1 (case 2) —A man aged 23 with pernicious anemia. The output of urobilinogen in the feces was determined before and after therapy with liver extract. Note the transient improvement after a single injection of liver extract and the secondary rise in the reticulocyte count, with continued improvement, after intensive therapy with liver extract. In this chart the values for the color index (*C I*) have been multiplied by 10, and the values for the mean corpuscular volume (*M C V*) in cubic microns have been divided by 10. In charts 1 to 4 the percentage values for hemoglobin (*Hb*) have been divided by 10, and the values for erythrocytes (*R B C*) have been divided by 1,000,000,

is of particular interest. The patient was given intramuscularly 1 cc of a concentrated liver extract, the amount derived from 100 Gm of whole liver. The reticulocyte count rose to 23 per cent on the fifth day after the injection, and there was a slight improvement in the blood

values coincident with a distinct decrease in the level of urobilinogen in the feces. This was only transient, for ten days later the excretion had again risen to the pretreatment level. With more intensive parenteral therapy with liver extract a second rise in the reticulocyte count occurred, and the urobilinogen content of the feces gradually dropped to a normal level, as did the icterus index, coincident with these changes the erythrocyte count and the hemoglobin value rose rapidly, while the color index and the mean corpuscular volume fell toward normal. It is of some interest that the output of urobilinogen remained well above

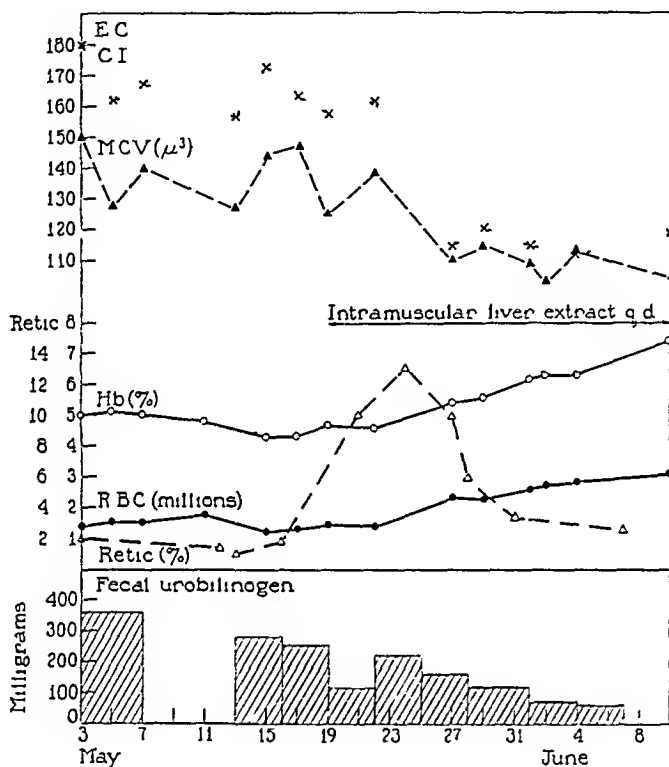


Chart 2 (case 5) —A woman aged 55 with pernicious anemia. Note the return of the output of urobilinogen to normal after intensive therapy with liver extract. In this chart the values for the color index (C I) have been multiplied by 100.

normal throughout the period of the reticulocyte response, that is, at a time when cell production and new hemoglobin formation were going on at a maximum rate. This observation, which is scarcely compatible with the theory of nonutilization, suggests that hemolysis was going on at an abnormally rapid rate even after active erythropoiesis had set in. In case 6 a similar situation was presented, with the output of pigment remaining well above normal even after a maximum reticulocyte response of 60 per cent.

Chart 2 also illustrates the progressive drop in the output of urobilinogen after the institution of therapy with liver extract in a case of relatively mild pernicious anemia.

Summary of Data

Case, Initials, Sex, Age	Diagnosis	Date	Erythrocytes, Millions	Hemoglobin, %	Leukocytes, Thousand	Mean Corpuscular			Fragility, %	Icteric Index	Serum Bilirubin, Mg per 100 Cc	Hepatic Function Tests			Comment
						Color Index	Volume, Cu Microns	Reticulocytes, %				1 Hour		Urobilinogen Excretion, Mg per Day	
												Bili rubin, Retention, %	Benzole Acid Excretion, Gm		
1 J B M, 40	Pernicious anemia	3/ 3/36	2 34	62	6 1	1 32	107	1 2	15	1 16	0	275	2 52	Before liver	
2 G B M, 23	Pernicious anemia	4/10/37	2 06	59	2 8	1 43	112	1 8	14	2 00	0	3 51	680	Before liver	
		5/11/37	1 10	36	2 9	1 61	127	6 2	15				1,050	Before liver	
		6/ 7/37	3 54	72	5 2	1 02	98	4 0	3				163	After liver (chart 1)	
3 C B * M, 64	Pernicious anemia	7/14/36	1 27	36	2 1	1 42	122	1 5	12	1 89	60	3 73	369	Before stomach U S P	
		7/30/36								1 62	5			After stomach U S P	
4 M C F, 36	Pernicious anemia	2/ 2/37	2 80	89	6 7	1 60	127	0 8	5	0 30	10	1 08	119	Before liver	
5 E O F, 55	Pernicious anemia	5/ 7/37	1 50	50	4 4	1 67	110	1 1	7				360	Before liver	
		6/ 4/37	2 82	63	5 9	1 12	114	2 1	6				76	After liver (chart 2)	
6 G C M, 61	Pernicious anemia	2/ 2/37	0 48	20	3 4	2 09	186	1 1	8	1 70	0	1 17	442 +	Before liver	
		2/17/37						60 0						Began liver, intramuscularly on 2/12	
		2/20/37	1 92	12	3 9	1 69	118	20 0					733	After liver	
		2/26/37	2 17	77	2 8	1 70	126	7 0	7				Trace	After liver	
		3/ 4/37	2 90	67	5 1	1 15	107	2 0				2 05	52	After liver	
		3/10/37	3 76	78	5 6	1 01	97	1 1	7				91	After liver	
7 F G M, 54	Pernicious anemia	11/14/35	2 12	71	3 6	1 68	130	1 1					305	Before liver therapy	
8 M L F, 65	Pernicious anemia	5/12/36	1 13	26	1 6	1 15	129	4 0	15	2 01			2 75	Before liver therapy, patient too constipated for satisfactory stool collection	
9 O M F, 71	Pernicious anemia	3/23/37	1 22	32	2 2	1 31	122	2 0	15	0 60	0		300	Before liver therapy	
		5/15/37	3 20	58	6 1	0 91	92	1 0	6				70	Two weeks after liver therapy	
		5/20/37	3 38	63	7 4	0 93	92	1 1	1				38	Three weeks after liver therapy	
10 E T M, 48	Pernicious anemia	10/22/36	1 23	40	3 6	1 63	147		10	3 00	41		201	Before liver therapy	
		11/27/36	2 40	64	3 7	1 28	128			1 63	0		12 72	Partial remission after liver extract patient constipated	
		12/ 2/36										3 15	295	Bowels regulated	

11 A C E, 31	Pernicious anemia of pregnancy	2/26/37	2 86	71	8 9	1 30	114	1 2	3	66	Trace	Before liver therapy
12 D S M, 56	Macrocytic anemia, intestinal anastomosis	1/ 9/36 2/19/37	2 13 1 88	60 88	2 1 7 1	1 41 0 80	131 82	2 0 1 0	4 5	1 86 3 45	0 21 0	Before treatment, diarrhea present. After treatment with liver extract and diet for sprue for 10 mo
13 M II M, 15	Tropical sprue	10/21/36 10/28/36 11/11/36 12/ 5/36	1 31	90	3 5	1 03	91	0 6	5	2 75	3 61 30 23	Stools pasty and gray Stools pasty but bet- ter color Stools pasty but bet ter color Stools pasty but bet ter color
14 D K F, 17	Tropical sprue	11/ 1/36 12/ 5/36 12/19/36	1 47	88	6 6	1 00	89		5		Trace Trace 83	Balanced diet, no liver extract Low protein diet, soft gray green stools After liver extract and diet for sprue, normal stools
15 J O E, 7	Congenital hemolytic jaundice	1/24/36 5/19/36 5/15/37	1 50 5 04 4 96	36 85 81	4 6 6 5 13 1	1 20 0 82 0 82	97 95 70	1 5 8 0 2 5 5	20 1 3		0 36 0 63 67	Before splenectomy Two weeks after splenectomy One year after splece- tomy, acute rheu- matic fever
16 M S F, 17	Congenital hemolytic jaundice	11/ 6/36 11/11/36 12/11/36 6/ 8/37	1 28 4 26 4 21 4 72	98 92 95 110	9 8 8 0 8 1 10 7	1 13 1 08 1 13 1 16	86 84 93 96	11 3 10 9 1 5 1 1	30 35 6 12	3 18	622+ 1,087 127 127	Before splenectomy Before splenectomy Two weeks after splenectomy Six months after splenectomy
17 E W M, 5	Congenital hemolytic jaundice	6/17/37 7/ 9/37	2 66 5 04	60 88	7 0 13 7	1 13 0 85	83 82	21 0 0 8	25 6		1 11 0 15	Before splenectomy Two weeks after splenectomy
18 P N M, 6	Hemolytic anemia, Cooley's type (?)	4/ 6/37 4/ 9/37 5/ 9/37 5/15/37	3 67 3 44 3 65 3 68	55 52 70 66	5 2 5 1 7 6 12 1	0 75 0 76 0 96 0 90	65 71 82 80	9 0 9 0 2 0 6 5	50 25 8 8		1 09 350 59 63	Before splenectomy Before splenectomy Two weeks after splenectomy Three weeks after splenectomy
19 A D M, 67	Acquired hemolytic anemia	2/ 5/37	1 81	53	6 5	1 46	132	9 8	15	3 90	0	No response to liver therapy
20 M L M, 23	Hemolytic anemia and purpura	7/22/36	2 18	51	2 4	1 17	101	12 0	9		1 54	Benzene poisoning, hyperplastic mar- row, later complete recovery

Summary of Data—Continued

Case, Initials, Sex, Age	Diagnosis	Date	Lymphocytes, Millions	Hemoglobin, %	Leukocytes, Thousands	Mean Corpuscular Volume, cμ	Color Index	Hepatic Function Tests				Comment			
								Serum Bilirubin, Mg per 100 cc	1 Hour Bilirubin Retention, %	4 Hour Benzoic Acid Excretion, Gm	Urobilinogen, Mg per Day				
													Fragility, %	Icteric Index	Fragility, %
21 O D M, 38	Hemolytic anemia and purpura	1/11/36	2.78	63	6.9	98	1.13	0.46	0.31	10	3.15	556	1.51	Marrow picture identical with that in case 20	
		2/ 7/36	2.00	46	33.6	99	1.15	12.8		15		1,000		Patient later died at another hospital with typical picture of acute myelogenous leukemia	
Group 3 Aplastic Anemias															
22 M A F, 36	Aplastic anemia	2/22/36	1.70	46	2.1		1.35			1		129	0.92	Hypoplastic fatty marrow	
23 V B F, 18	Aplastic anemia	7/18/36	1.58	33	1.6	88	1.04	0.5		6		119	1.82	Hypoplastic fatty marrow	
24 S B M, 44	Aplastic anemia due to benzene	11/ 1/35	0.60	12	1.1	80	1.00	1.0		1		85		Hypoplastic fatty marrow	
25 R B F, 27	Aplastic anemia due to arsphenamine	10/30/36	1.21	30	1.9	100	1.21	1.6		10	6	111	16.60	Hypoplastic fatty marrow	
26 J B F, 59	Aplastic anemia due to hair dye (?)	12/10/35	1.21	31	2.1	105	1.28	1.0	0.46	6	3.60	2.0	2.72	Hypoplastic fatty marrow, presplenectomy values	
		3/25/36	1.99	46	2.2	103	1.15	2.8		5		60	1.92	Six weeks after splenectomy	
		10/13/36	0.82	20	1.6	123	1.22	1.7		5	9	20	1.06	Eight months after splenectomy	
27 A C M, 19	Aplastic anemia due to hydroquinone (?)	2/20/27	0.65	17	2.8	123	1.30	1.8	0.41	6		108	0.94	Hypoplastic fatty marrow, 3 day period before transfusion	
		3/23/37	0.67	19	1.6			2.1				600		Three day period after transfusion (chart 3)	
28 H D F, 66	Aplastic anemia	12/10/35	1.83	40	2.8	94	1.09	0.2		3	3.62	86		Hypoplastic fatty marrow	
29 F H M, 59	Aplastic anemia due to benzene (?)	5/ 8/36	1.06	27	3.1	119	1.27	3.5	0.41	3		83	0.97	Hypoplastic fatty marrow	

30 M J F, 13	Aplastic anemia	6/15/37	1 30	35	1 3	1 35	106	2 3	7	189	Trace
31 T M M, 51	Aplastic anemia	11/ 1/35	0 80	19	1 9	1 10	110	3 6	15	163	Hypoplastic fatty marrow
32 E S F, 19	Aplastic anemia due to benzene	3/10/37 1/10/37	2 52 1 79	63 51	5 9 3 7	1 25 1 12	101 109	3 7 1 0	7 5	232 197	Trace Hypoplastic fatty marrow
33 E T M, 63	Aplastic ane- mia, miliary tuberculosis	5/19/36	2 17	51	1 5	1 03	96		5	62	1 85 Normally cellular mar- row with arrest of maturation
34 S B F, 25	Aplastic anemia	10/10/36 1/28/37	2 61 3 30	57 63	3 9 10 5	1 03 0 95	96 98	2 2	5 2	21 3 66	0 51 Immature cellular marrow
35 A D M, 53	Aplastic anemia	11/11/35	1 19	21	1 3	0 83	81	1 6		272	Immature cellular marrow
36 W G M, 26	Aplastic anemia	11/11/36	2 00	10	2 1	1 00		0 8	0 12 0 28	272	1 25 Immature cellular marrow hemo- chromatosis
37 D L M, 26	Aplastic anemia	1/28/37 5/ 7/37	1 10 1 23	35 29	1 1 1 5	1 23 1 18	97 91	1 2 2 1	5 5	212 76	0 55 First urobilinogen determination, 5 days after transfu- sion, with chill Second determination, 2 weeks after trans- fusion, immature cellular marrow with large hyperplastic nodules
38 G M M, 31	Aplastic anemia due to roentgen rays (?)	9/30/36 12/ 2/36 3/ 1/37 6/15/37	1 31 1 43 1 67 1 17	26 31 30 26	1 0 0 9 1 1 3 3	1 00 1 09 0 90 1 11	90 93 79	3 8 2 5 2 3 2 5		300 380 130 177	1 05 Immature cellular marrow 3 32 Before splenectomy 1 11 Seven weeks after splenectomy 1 69 16 08 1 light weeks after splenectomy, 5 weeks after transfusion (chart 1)
39 F M M, 47	Aplastic anemia	5/ 7/37	3 23	81	2 5	1 30	110	1 1	5	120	0 81 Immature cellular marrow
40 R M M, 21	Aplastic anemia, hemo- chromatosis	11/ 1/35	1 29	21	2 5	0 82	102			172	Immature cellular marrow, hemo- chromatosis
41 C S F, 53	Aplastic anemia due to bilir dye (?)	3/16/37 1/ 2/37	1 60 1 81	10 37	2 3 1 4	1 25 1 00	92 91	1 0 0 4	5 8	133 101	Trace Immature cellular marrow

Summary of Data—Continued

Case, Initials, Sex, Age	Diagnosis	Date	Lrythrocytes, Mil g'lons	Hemo- globin, %	Leuko- cytes, Thou- sands	Color Index	Mean Corpuscular Volume, Cu Microns	Reticu- lo- cytes, %	Fragility, %	Icteric Index	Hepatic Func- tion Tests				Comment
											Serum Bilirubin, Mg per 100 Cc	4 Hour Bilirubin Reten- tion, %	4 Hour Benzoid Acid Excre- tion, Gm	Urobilinogen Excretion, Mg per Day	
42 P S M, 60	Aplastic anemia	5/24/37	1 76	47	4 3	1 33	102	1 8	Group 3 Aplastic Anemias--Continued				265	Immature cellular marrow	
43 F Y F, 30	Aplastic anemia	12/ 9/36	2 21	60	2 8	1 49	130	2 3	0 44-0 34	5	0 75	0	3 08	98	Immature cellular marrow
44 J L M, 47	Aplastic anemia	1/26/37	1 03	24	1 5	1 17	104	3 6	0 44-0 34	3	0 60	4	3 25	235	Hodgkin's type of marrow
45 A P M, 53	Aplastic anemia	2/12/37	3 12	69	1 3	1 10	86	4 0		100	2 00	0	2 21	52	Hodgkin's disease of liver, spleen and bone marrow
46 A L M, 18	Aplastic anemia	2/19/36	1 64	36	5 7	1 10	93	1 0	0 46-0 34	6	0 52	21	3 61	178	Sclerotic bone marrow, marked hepatosplenomegaly
47 C D M, 65	Chronic myelogenous leukemia	10/13/36 11/ 6/36	1 52 1 69	26 32	3 6 1 0	0 86 0 95	81 97			6	0 29 1	6		175 27 70	
48 J H F, 18	Chronic myelogenous leukemia	1/30/37	2 63	50	172 0	0 95	87	7 6	Group 4 Leukemias				298	0 95	
49 F F F, 56	Chronic myelogenous leukemia	12/16/36	3 42	70	212 0	1 02	82	3 5		5				23	0 89
50 F G M, 63	Chronic myelogenous leukemia	6/23/36	1 03	28	6 1	1 36	121	3 2		11				169	8 70
51 V G F, 18	Chronic myelogenous leukemia	4/17/37	1 22	35	0 6	1 13	118	3 1		3	0 50	23	2 83	75	0 17
52 P H F, 72	Chronic myelogenous leukemia due to hair dye (?)	7/10/36	1 00	32	3 0	1 60	125	1 2		3	0 52	0		32	0 43
53 P H F, 72	Chronic myelogenous leukemia	5/26/36	1 60	33	2 7	1 03	80	0 2		3	0 38	1		101	Trace

		3/3/36	1/39	12	11 S	1/51	121	6/2	0 18 0 38	S	560	Trace
53 D M M, 11	Alukemic mycogenous leukemia											
54 R T M, 15	Alukemic mycogenous leukemia	5/15/36	1 00	82	2 1	1 03	88		0 67	13	2 63	101 0 92
55 I B M, 31	Chronic lymphatic leukemia	6/ 8/37	2 71	60	16 9	1 10	88	1 6	0 55	9	3 66	210 2 20
Group 5 Miscellaneous Conditions												
56 H P F, 70	Nutritional hypochromic microcytic anemia	6/24/36	3 80	59	1 8	0 78	77	4 0		2	67	0 35
57 J S M, 59	Carcinoma of stomach, hypochromic microcytic anemia	6/10/37	3 00	39	7 3	0 65					87	0
58 V L F, 16	Banti's syndrome	10/11/36 12/16/36	1 11 5 10	70 85	2 1 8 0	0 85 0 83	75	2 5	0 11 0 30	3	10 19) 2 25 3 06	0 16 0 17
59 B L M, 61	Banti's syndrome	12/19/36	4 60	80	2 8	0 87		1 8		3	3 05	2 60
60 L S F, 23	Banti's syndrome	3/ 3/36 3/31/36	3 17 3 98	45 78	2 0 2 0	0 71 0 98	65 92	2 8 2 0	0 46 0 28	6 10	2 52 2 4	0 86 0 37
61 N S F, 33	Banti's syndrome, hemangioma of spleen	10/21/36 2/22/36	2 14 4 18	50 67	2 9 4 1	1 17 0 80	89 75	1 4 1 6	1 37 0 31	10 4	2 68 2 53	0 37
62 L T M, 20	Banti's syndrome	9/16/36 10/28/36 1/18/37	3 73 5 24 4 83	59 84 73	5 9 3 1 7 5	0 79 0 80 0 76	78 82	2 4 1 0	1 10 0 10	5 8 11	2 92 3 28 3 50	3 07 2 83 0 87
63 M O F, 14	Thrombopenic purpura	2/12/37	1 76	81	8 2	0 85	90	2 1		1	3 55	0 31
64 R G M, 59	Polycythemia vera	6/16/36	4 56	91	10 5	1 03	91	3 0		8		Trace

Before iron
Platelets, 58,000
Four weeks after
splenectomy, plate
lets, 1,100,000
Before splenectomy,
platelets, 106,000
Before iron
Three weeks after
starting iron
One week after second
large hematemeses
Before splenectomy,
platelets, 60,000
Before iron
After iron
Two months after
splenectomy and
recovery from severe
postoperative
hemorrhage
Platelets, 11,000

Summary of Data—Continued

Case, Initials, Sex, Age	Diagnosis	Date	Dry thro cytes, Ml lions	Hemo globin, %	Leuko cytes, Thou sands	Color Index	Mean Corpus cular Volume, Cu Microns	Retic ulo cytes, %	Miscellaneous—Continued	Hepatic function Tests				Comment			
										Serum Bili rubin, Mg per 100 Ce	1 Hour Bili rubin Reten tion, %	4 Hour Benzole Acid Excre tion, Gm	Urobilinogen Excretion, Mg per Day				
															Fragility, Icteric Index	Fecal	Urinary
65 A P F, 48	Polyeythaemia vera	5/26/36 6/6/36 6/19/36	8.12 6.85 7.40	168 146 160	7.9 9.2 9.9	1.03 1.07 1.08	93 102 97	1.6	0.46-0.32	6			Trace Trace 0.55	Before treatment After venesection After acetylphenyl hydrazine, 0.1 Gm four times daily for 1 week			
66 O B F, 44	Cirrhosis of liver	3/14/36 5/27/36 9/30/36 11/6/36 2/12/37	2.30 3.05 2.96 2.95 3.08	58 70 72 72 66	6.6 4.6 6.0 4.9 4.6	1.26 1.15 1.22 1.22 1.07	111 100 108 108 106			20 15 15 15 50	2.92 1.39 1.25	45 16 2 20	8.72 5.60 5.00 10.70 9.24	Trace	After phenylhydrazine hydrochloride, 0.1 Gm four times daily for 11 days		
67 F K F, 33	Cirrhosis of liver, cholangitis	3/10/37	3.53	82	5.0	1.16	98	3.0	0.42-0.28				1.75	24.60			
68 S M F, 50	Cirrhosis of liver	5/11/37	3.21	62	5.7	0.97	85	2.4		5	0.25 0.20	9 6	1.86 2.04	0.89			
69 R P M, 13	Cirrhosis of liver, nephritis	2/1/36	2.31	43	9.9	0.93	82			15	1.60	33	0.94	4.73			
70 P R M, 41	Chronic arsenic poison ing, cirrhosis of liver (?)	2/5/37	4.17	88	6.2	1.05	88	1.9	0.42-0.30	7	0.50	5	3.66	8.9	1.65		
71 M W M, 62	Cirrhosis of liver	1/9/36	2.22	70	5.9	1.12	101	0.6	0.16-0.32	1			2.67 1.71	0.81			
72 M M M, 35	Abdominal Hodgkin's disease	6/15/37	1.20	89	2.5	1.06	88	1.2		5				1.34			
73 N S M, 26	Gaucher's disease	5/12/36	1.81	90	2.9	0.93	90				1.35	0		2.20	1.28		
74 W A F, 25	Chronic nephritis, uremia	11/1/36	3.30	75	10.6	1.11	92	1.0						55	Nonprotein nitrogen, 62 mg. per 100 cc., urea clearance, 11 per cent of normal		

Nonprotein nitrogen,
62 mg per 100 cc,
urea clearance, 11 per
cent of normal

The excretion of urobilinogen in the urine was increased in 5 cases and was normal in 4 cases of pernicious anemia in relapse. In case 6, when the urobilinogen in the urine was followed before and after therapy with liver extract, the level fell rapidly to a low normal value.

The patient with pernicious anemia of pregnancy (case 11) showed low values for urobilinogen in both feces and urine.

In the case of macrocytic anemia associated with intestinal anastomosis (case 12) it was impossible to obtain satisfactory collections of stool because of diarrhea. However, the low icterus index and the low value for urobilinogen in the urine may be regarded as evidence against excessive hemolysis.

Two patients with tropical sprue gave low values for urobilinogen in the feces at a time when the stools were pasty and gray-white but not actively diarrheal. For 1 patient (case 13) an average daily value of only 3 mg of urobilinogen was obtained for the feces, with only a trace of urobilinogen appearing in the urine. A qualitative test for unchanged bilirubin gave a negative reaction. Since there was no jaundice or other evidence of retention of bile, it seemed probable that the pigment was being excreted in a nondetectable form. Manson-Bahr¹² has stated that sprue stools have a light color, not because of a decrease in the amount of bile pigment excreted but because the pigment is excreted in a colorless reduced state as urobilinogen. The correctness of this hypothesis is open to question. (1) because sprue stools tend to maintain their light color even after exposure to air and sunlight, whereas urobilinogen should be oxidized to red-brown urobilin under such conditions, (2) because such an exceedingly low value for bile pigment in typical sprue stools has been obtained with a method designed for determination of the urobilinogen quantitatively.

Bilirubin excretion tests of hepatic function were performed on 7 of the 10 patients with pernicious anemia. Three patients showed a four-hour retention of more than 5 per cent, however, since the original bilirubin level of the serum was above 1 mg per hundred cubic centimeters in 2 of these cases, extreme caution must be taken in interpreting the results as evidence of hepatic damage.⁸ It is somewhat puzzling that there was no retention of bilirubin in 4 cases in which the original bilirubin level of the serum was above 1 mg per hundred cubic centimeters. The patient with the intestinal anastomosis and 1 patient with tropical sprue excreted bilirubin normally.

Variable results were obtained with the hippuric acid synthesis test for this group of patients. Three patients with pernicious anemia (2 had not been treated and 1 had been) gave normal results, whereas

¹² Manson-Bahr, P. H. *Manson's Tropical Diseases*, ed. 10. Baltimore, William Wood & Company, 1936.

2 gave low results. For 1 of the latter (case 6) the amount of hippuric acid excreted rose somewhat after the administration of liver extract but still remained well below normal. Fouts, Helmer and Zerfas¹³ found a reduction in the excretion of hippuric acid in the majority of their cases of pernicious anemia in relapse, with variable improvement after treatment. The excretion of hippuric acid was somewhat lower than normal in 1 case of tropical spleen (case 13) and was even lower in the case of macrocytic anemia associated with intestinal anastomosis. Poor absorption of the sodium benzoate from the intestinal tract may well have been a factor in these 2 cases. In the latter case a normal result was obtained after the diarrhea had been controlled by appropriate therapy.

Group 2 Hemolytic Anemias—The excretion of urobilinogen was studied in 7 cases of hemolytic anemia—3 cases of typical congenital hemolytic jaundice, 1 case of questionable erythroblastic anemia (case 18), 1 case of severe chronic hemolytic anemia of undetermined etiology (case 19) and 2 cases of acute hemolytic anemia presumably due to benzene poisoning. Well marked anemia was present in 6 of the 7 cases. All 7 cases were characterized by jaundice, splenomegaly, a high icterus index and reticulocytosis, increased fragility of the red blood cells was present in the 3 cases of congenital hemolytic jaundice and in the case in which chronic hemolytic anemia developed late in life.

The striking feature in all 7 cases was a marked increase in urobilinogen in the feces, varying from 350 mg a day in case 18 (a boy of 6 years) to 1,517 mg a day in case 19. The urobilinogen in the urine was definitely increased in only 2 cases.

Splenectomy was performed in the 3 cases of congenital hemolytic jaundice, in each case the urobilinogen in the feces dropped to a low normal value within two weeks after operation. The output of urobilinogen was still within normal limits one year later in case 15 and six months later in case 16. Coincident with the drop in urobilinogen value, the erythrocyte count and the hemoglobin level rose, and the icterus index and the reticulocyte count fell to normal. Erythrocyte fragility remained abnormal, although there was a tendency for the minimum resistance to return toward normal in cases 15 and 16.

Case 18 was that of a Greek boy aged 6, who presented a clinical picture of jaundice, hypochromic microcytic anemia, hyperbilirubinemia, reticulocytosis and increased output of pigment with decreased fragility of the erythrocytes, in contrast to the cases of congenital hemolytic icterus. The absence of nucleated red cells in the peripheral blood and the lack of characteristic skeletal changes cast some doubt on the diag-

¹³ Fouts, P. J., Helmer, O. M., and Zerfas, L. G. The Secretion of Hippuric Acid in Pernicious Anemia, *Am J M Sc* **193** 647-652, 1937.

nosis of erythroblastic anemia, although the sternal bone marrow presented a picture of normoerythroblastic hyperplasia. After treatment with liver and iron preparations had failed to improve the blood picture during a one year period of observation, it was decided to perform splenectomy in the hope of decreasing the rate of hemolysis. The immediate result was gratifying, as shown in the accompanying table, however, the erythrocyte count, hemoglobin value and reticulocyte percentage gradually returned to preoperative levels, and the icterus index slowly rose after the patient was discharged from the hospital. The urobilinogen determination three weeks postoperatively was essentially normal, suggesting that splenectomy had stopped temporarily the excessive hemolysis. However, the subsequent course made it appear that other organs had taken over the function of red blood cell destruction, unfortunately it was not possible to carry out further studies of the excretion of pigment to confirm this impression.

The bilirubin excretion test of hepatic function was performed on only 1 patient of the group (case 19), in whom hepatic damage was suspected. Although the serum bilirubin value was 1.63 mg per hundred cubic centimeters, there was no retention of the injected bilirubin after four hours. This result is comparable to that obtained in certain cases of pernicious anemia in relapse.

The hippuric acid test gave normal results for the 3 patients tested (cases 16, 19 and 21).

Group 3 Aplastic Anemias—Aplastic anemia is used here in the broad sense to include anemia that is refractory to any known form of therapy in which the bone marrow is (1) hypoplastic to aplastic, (2) cellular but immature, (3) of Hodgkin's type or (4) sclerotic. Twenty-five patients make up this group.

One or more determinations of the output of urobilinogen in the feces were made in all 25 cases, and the output of urobilinogen in the urine was determined in 19 of the cases. In only 8 of the 25 cases were the values for urobilinogen in the feces above Watson's upper limit of normal, and in 6 of the 8 the increase was slight. In the great majority of the cases the values were well within normal limits, abnormally low values were rarely encountered. Urobilinogen in the urine was within normal limits in 13 of the 19 cases studied, in 2 cases (cases 26 and 38) there was elevation of the urobilinogen in the urine proportional to the increase in urobilinogen in the feces, whereas in 4 cases (cases 25, 44, 45 and 46) there was a well marked increase in urobilinogen in the urine, with normal values for the feces. The increased urobilinuria suggested hepatic damage in these 4 cases, and this suggestion was borne out by further evidence of hepatic dysfunction in 3 of the 4.

The output of urobilinogen in the feces was followed over a prolonged period in 1 case (case 27) of aplastic anemia in which there was hypoplastic fatty marrow (chart 3). A sharp increase in the rate of excretion of urobilinogen followed each blood transfusion. It had been noted that the improvement in the blood picture following transfusion was transient, an observation which suggested that the patient was hemolyzing transfused blood. The urobilinogen values before and after a transfusion supported this hypothesis. On one occasion the average daily value for urobilinogen in the feces rose from 108 mg during the three-day period before the transfusion to 600 mg during the corresponding period immediately after the transfusion. The excretion of pigment then decreased gradually to the original level until after the

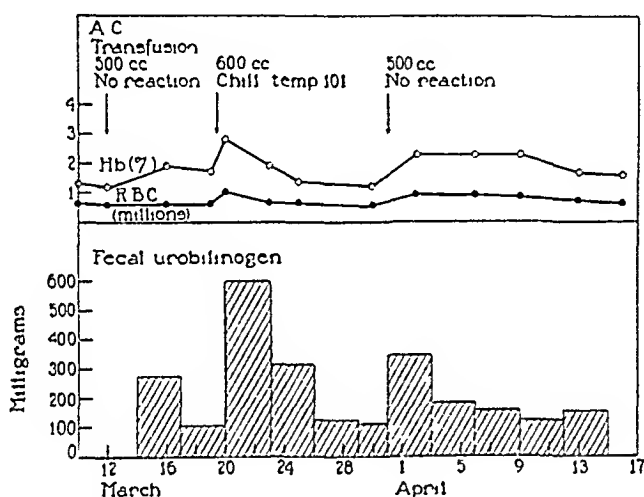


Chart 3 (case 27)—A man aged 19 with aplastic anemia showed hypoplastic bone marrow. The chart illustrates the striking increase in the output of urobilinogen following transfusions.

next transfusion. This was followed by a sharp though less pronounced rise in the urobilinogen in the feces to 350 mg a day. The chart shows that the improvement in the hemoglobin level was maintained over a longer period after the second transfusion, apparently because less of the transfused blood was lost through hemolysis. Since there was a febrile reaction to the first transfusion and no reaction to the second, it is conceivable that either fever or the sudden hemolysis of a large number of the transfused cells may have been responsible for the increased excretion of pigment. At each transfusion whole blood was given by the direct multiple syringe method, 2 different donors of the same blood group as the patient being used. In view of the increase in output of pigment following a blood transfusion, it is obviously advisable to wait at least a week after a transfusion before beginning to collect stool for study of the urobilinogen, otherwise a false high value

may be obtained. As a further illustration of this principle, in case 37 two determinations of urobilinogen in the feces were carried out. The first collection period ran from the second to the fifth day after a transfusion, and a rather high average daily value, 212 mg, was obtained. During a second collection period, two weeks after the transfusion, the average output was much lower, 76 mg a day.

The details of the clinical course of this group of patients will be discussed elsewhere¹⁴. However, the 2 patients of the group who were subjected to splenectomy (cases 26 and 38) may be briefly mentioned here. In each case the presence of abnormally large amounts of urobilinogen in the feces suggested that a hemolytic factor was playing a role in the production of the anemia. After various forms of medical therapy had proved ineffective, it seemed justifiable to remove the spleen in the hope of decreasing the rate of hemolysis. In case 26 the output of urobilinogen dropped from a preoperative level of 230 mg a day to 60 mg six weeks postoperatively. The patient was able to go five months without a transfusion, whereas for six months prior to operation she had required one transfusion a month. Eight months after splenectomy the value for urobilinogen in the feces was extremely low, 20 mg a day. Thus splenectomy appeared to remove a hemolytic factor and thereby to bring about temporary improvement, yet the ultimate outcome of the disease was the usual one, with death occurring from intercurrent infection nine months after the operation.

The other splenectomized patient (case 38) has not been observed over a sufficiently long postoperative period to allow of definite conclusions as to the value of the operation. He was first followed over a period of six months, during which therapy with various hemopoietic agents failed to modify the course of his illness to any appreciable extent. Transfusions were given at intervals of three to four weeks. Multiple determinations of urobilinogen were made for this patient (chart 4). It is of interest that practically all the preoperative values obtained were well above the upper limit of normal. Values within normal limits were obtained after the first course of liver extract was given parenterally, although there was no improvement in the blood level during this period, furthermore, a second course of parenteral treatment with liver extract exerted no appreciable effect on the abnormally high level of urobilinogen. All that can be said at present of the effect of splenectomy in this case is that the patient seemed distinctly improved, after eight months of hospitalization, the majority of the time being spent in bed, he was able to be up and about and to go home, even though a severe grade of anemia was still present. Two determina-

14 Rhoads, C. P., Miller, D. K., and Barker, W. H. Unpublished data.

tions of urobilinogen, made six and seven weeks, respectively, after operation, gave values near the upper limit of normal, suggesting that hemolysis had been reduced

For 4 patients with normal values for urobilinogen in the feces (cases 25, 44, 45 and 46) the values for urobilinogen in the urine were distinctly above normal, suggestive of hepatic dysfunction. In 3 of the 4 cases there was further evidence of hepatic dysfunction from other tests. In 15 cases of aplastic anemia the urobilinogen value for the urine was either normal or elevated in proportion to the fecal value.

Hepatic function tests were performed on 16 of the 25 patients in this group. Seven patients gave normal results for both the bilirubin excretion test and the hippuric acid synthesis test, 1 patient gave a

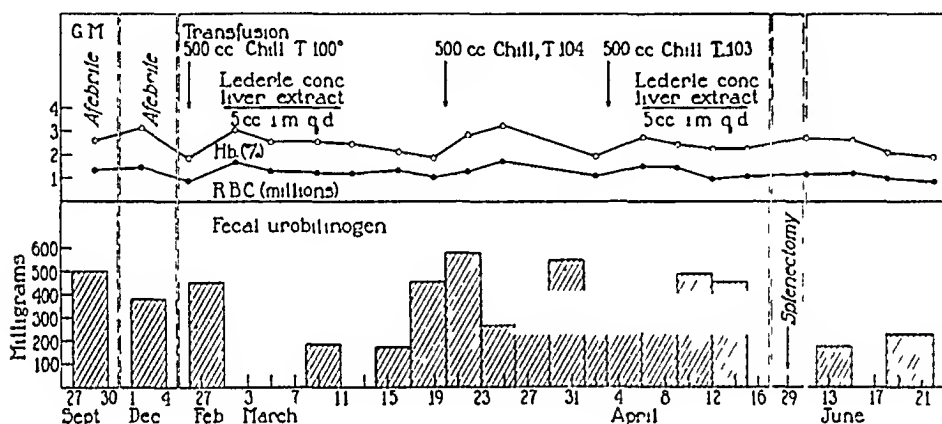


Chart 4 (case 38) —A man aged 34 with aplastic anemia showed immature cellular marrow. The output of urobilinogen in the feces remained well above normal over a prolonged period, suggesting excessive hemolysis. There was an apparent reduction in the rate of hemolysis after splenectomy.

normal result for the only test performed and 8 showed evidence of hepatic damage. A four-hour bilirubin retention above 5 per cent was present in 6 cases, a four-hour excretion of benzoic acid below 3 Gm, in 4 cases, and evidence of hepatic dysfunction by both tests, in only 2 cases. Thus 50 per cent of the patients on whom hepatic function tests were performed gave evidence of hepatic damage. There does not appear to be a definite association between the type of marrow and the hepatic dysfunction.

Tests of erythrocyte fragility were carried out in 13 of the 25 cases. In 10 cases there was a normal range, in 1, slightly increased fragility (case 31), and in 2, somewhat decreased fragility (cases 36 and 37).

Group 4 Leukemias —Determinations of urobilinogen in the urine and in the feces were made for 9 patients suffering from various forms of leukemia. The value for the feces was definitely elevated in 2 cases

(cases 47 and 53) It is well to recall here case 21, discussed earlier in connection with the cases of hemolytic anemia This patient showed severe hemolytic anemia with purpura after exposure to benzene and subsequently died of acute myelogenous leukemia When he was seen two months before death, the clinical findings and the picture of the bone marrow were those of hemolytic anemia, and proof of leukemia was not at hand Attention has been directed to the presence of hemolytic anemia in association with leukemia by several authors, among them Jaffé¹⁵ and Beltrametti and his associates¹⁶ In other cases of leukemia the anemia appears to be due entirely to the replacement of erythroid with myeloid tissue This was probably the case in the other patients of this group, for whom the output of pigment was either normal (cases 49, 50, 52, 54 and 55) or unusually low (cases 48 and 51)

The urobilinogen content of the urine was elevated in 2 cases (cases 49 and 55), with normal values for the feces, once more suggesting hepatic dysfunction

The incidence of hepatic dysfunction was high for the group of patients with leukemia, 3 of the 6 patients tested showed abnormal four-hour retention of bilirubin, and 3 of the 4 patients tested showed a four-hour excretion of benzoic acid below 3 Gm

Group 5 Miscellaneous Conditions—This group includes patients with several different forms of blood dyscrasia who cannot be included in the four other groups There were 2 cases of chronic hypochromic microcytic anemia, 5 cases of Banti's syndrome 2 cases of polycythaemia vera, 6 cases of cirrhosis of the liver and 1 case each of thrombopenic purpura, abdominal Hodgkin's disease with leukopenia, Gaucher's disease and chronic nephritis with uremia

For 18 of the 19 patients in the group the output of urobilinogen in the feces was determined In 1 case of Banti's syndrome (case 59) and 1 case of polycythemia (case 64) there was a slight elevation of the urobilinogen in the feces above normal, in the other 16 cases the values were normal or low (case 56 and 60) In case 65 (that of a woman with polycythaemia vera) the output of urobilinogen was studied before and after therapy with phenylhydrazine The condition proved refractory to the treatment in the dosage used, and there was a relatively slight rise in excretion of pigment, which was reflected in lack of appreciable improvement in the blood picture

The low value for urobilinogen in the feces in the case of uremia (case 74) suggests that the refractory anemia of chronic nephritis is aplastic rather than hemolytic

15 Jaffé, R. H. Erythropoiesis in Leukemia, *Folia haemat* 49 51-63, 1933

16 Beltrametti, L. Rettanni, G., and Bascape, A. L'anemia nelle leucemie, *Haematologica* 18 337-370, 1937

The average daily excretion of urobilinogen in the urine was determined for 17 of the 19 patients of the group. In 2 cases of Banti's syndrome (case 59 and 62) and in 3 of the 6 cases of hepatic cirrhosis (cases 66, 67 and 69) the excess of urobilinogen in the urine in the presence of normal quantities in the feces may be regarded as evidence of hepatic damage. It is of interest that the quantity in the urine returned to normal after splenectomy in 1 case of Banti's syndrome (case 62).

In only 1 of the 5 cases of Banti's syndrome was there failure to show evidence of hepatic damage by at least one of the two hepatic

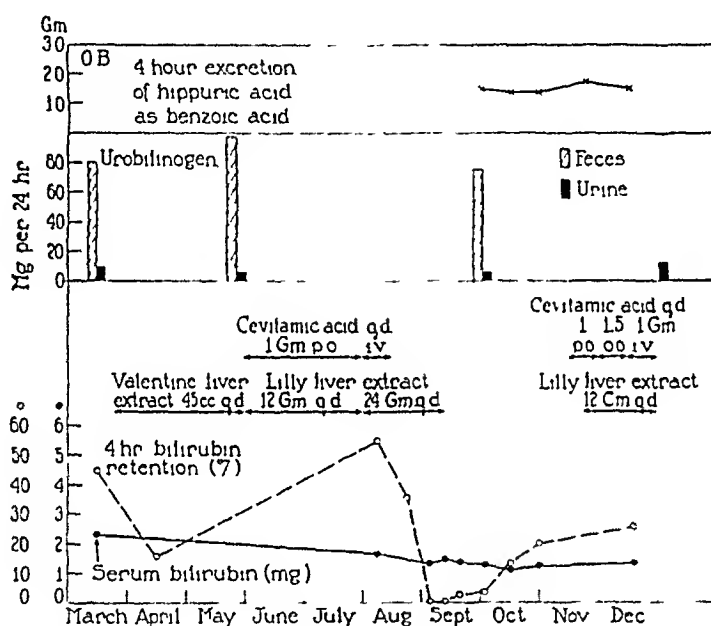


Chart 5 (case 66) —A woman aged 44 had cirrhosis of the liver and macrocytic anemia. The hepatic function and the excretion of urobilinogen were followed for nine months.

function tests employed. In 4 cases there was low excretion of hippuric acid and in 1 case (case 60) marked retention of bilirubin as well. The excretion of hippuric acid rose to normal after splenectomy in 2 cases (cases 58 and 62).

In 5 of the 6 cases of suspected cirrhosis of the liver, evidence of hepatic dysfunction was shown by at least one of the two tests. A four-hour excretion of benzoic acid of only 0.84 Gm was found in 1 case (case 69), but impaired renal function was probably a factor contributing to this low value.

In another case of cirrhosis of the liver (case 66) the results of repeated hepatic function tests have been charted over a relatively long period, with the urobilinogen values determined at intervals (chart 5). The excretion of benzoic acid remained remarkably constant between

1.4 and 2 Gm in four hours, urea clearance was normal in this case, and there was no apparent interference with intestinal absorption, so that the abnormally low excretion of hippuric acid here may be accepted as evidence of poor hepatic function. The four-hour retention of bilirubin fluctuated widely with different tests, from 0 to 55 per cent. Since the serum bilirubin value was constantly elevated above 1 mg per hundred cubic centimeters, the results are difficult to interpret. The absence of bilirubin retention, as shown by two tests, even though the serum bilirubin value was elevated above 1 mg per hundred cubic centimeters, is also confusing. Similar results were obtained in certain cases of pernicious anemia previously discussed. It is conceivable that under some conditions the hepatic threshold for serum bilirubin becomes stabilized at a level considerably higher than normal and that the liver varies in its power to excrete an amount of bilirubin raising the serum level above the new threshold. In the case under discussion the urobilinogen in the feces remained quite constant at a low normal level, between 75 and 90 mg a day. The urobilinogen in the urine was always well above normal, varying from 5.6 to 10.7 mg a day. This constant elevation of the urobilinogen in the urine, with normal values for the feces, gave additional evidence of severe hepatic damage in this case. Therapy with liver extract and ascorbic acid appeared to benefit the patient considerably, but no objective evidence of improved hepatic function was obtained unless the drop in retention of bilirubin may be accepted as such.

Erythrocyte fragility was studied in 3 cases of Banti's syndrome, 3 cases of cirrhosis of the liver and 1 case of polycythemia. Although the minimum resistance (the point at which hemolysis begins) was normal, the maximum resistance was increased in all 7 cases to between 0.32 and 0.28 per cent.

COMMENT

This study of the excretion of bile pigment in 74 cases of disease of the blood was made to investigate the role of destruction of blood in the production of anemia. Although it has been suggested that bile pigment may be produced through some independent activity of the liver and need not be derived from hemoglobin, no proof for this hypothesis is furnished, and the majority of workers are inclined to accept the theory that the hemoglobin of the blood is the sole source of bile pigment. Except in the presence of hepatic disease or of obstruction to the biliary tract, practically all the bile pigment excreted appears as stercobilin in the feces. The stercobilin can be quantitated with considerable accuracy by Watson's modification of the Terwen method, the result being expressed in terms of urobilinogen. The average daily output of urobilinogen in the feces may then be regarded as an index of the breakdown of hemoglobin or the destruction of blood.

A marked increase in the output of urobilinogen in the feces was the rule for two groups of patients with blood dyscrasias—those with pernicious anemia in relapse and those with hemolytic anemia. The quantity of urobilinogen excreted in a case of severe pernicious anemia in relapse may be just as great as that in a case of congenital hemolytic jaundice. The occurrence of increased destruction of blood in congenital hemolytic jaundice is universally accepted, and it seems as logical to accept excessive hemolysis as an important factor in pernicious anemia. There is no adequate proof as to whether the increased destruction of blood in pernicious anemia is due to the presence of large numbers of abnormal erythrocytes which are readily destroyed by the normal breakdown mechanism of the body or to the activity of a circulating hemolytic toxin.

The observations on pigment metabolism in the aplastic anemias and the hypochromic microcytic anemias furnish further evidence against the nonutilization theory of excessive excretion of pigment in pernicious anemia. Normal or low values for urobilinogen in the feces were obtained in most cases of aplastic anemia and in all cases of hypochromic microcytic anemia studied. In the aplastic anemias, cell formation is obviously inadequate, and in the hypochromic anemias the production of new hemoglobin is depressed. Unless destruction of blood is far below normal in such cases, according to the nonutilization theory, one might expect an output of pigment far above normal, yet the opposite is the case. That a marked decrease in destruction of blood should occur in such cases appears no more likely than the possibility of a marked increase in destruction of blood in pernicious anemia.

Certain other points of interest arose in the course of this study of excretion of urobilinogen. The picture of acute hemolytic anemia has been found to occur occasionally in association with acute leukemia, confirming the observation of previous workers on the subject. Of particular interest were 2 cases of benzene poisoning with hemolytic anemia and purpura, 1 patient made a complete recovery, and the other died of acute myelogenous leukemia. Cabot and Mallory¹⁷ have reported a somewhat similar case of fatal hemolytic anemia, which they attributed to benzene poisoning. Since benzene is fairly well established as one cause of clinical thrombopenic purpura and aplastic anemia, as well as of experimental granulopenia and leukemia, it appears likely that this aromatic compound may cause almost any conceivable type of bone marrow disturbance. If this should prove to be the case, it would bring the hemolytic anemias, the aplastic anemias, the leukemias, the granulopenias and the purpuras much closer together from the etiologic

17 Benzol Poisoning with Bleeding Gums, Hemolytic Anemia, and Active Marrow, Cabot Case 13321, Boston M & S J 197 236-239, 1927

standpoint, that is, these various forms of blood dyscrasia might be regarded as different types of response to a single chemical toxin or to closely related aromatic compounds

The rapid hemolysis of transfused blood, as shown by a sharp rise in the excretion of urobilinogen in the feces after transfusion, deserves further consideration here. This phenomenon probably furnishes an explanation for the failure of many patients with severe anemia to derive more than transient benefit from a transfusion. Also it serves as a warning in interpreting the results of determinations of urobilinogen carried out shortly after a transfusion, for if stools are collected during a period immediately after a transfusion, a value may be obtained that is much higher than the true "basal" value for the particular patient. It is advisable to wait at least ten days to two weeks after a transfusion before starting stool collections for determination of the urobilinogen excretion.

In certain cases of refractory anemia a high urobilinogen value in the feces, serving as an index of increased destruction of blood, may justify splenectomy as a therapeutic measure with the hope of cutting hemolysis down to a minimum and thereby eliminating a hemolytic factor. In 2 such cases splenectomy was followed by sufficient evidence of improvement to warrant further trial in selected cases.

The urobilinogen in the urine may or may not be increased in proportion to the urobilinogen in the feces. The value for the urine is therefore not a safe index of increased excretion of pigment or of increased destruction of blood, it is of more value as an index of hepatic function, for an increased quantity in the urine in the presence of a low or normal amount in the feces may be regarded as conclusive evidence of hepatic dysfunction, as Watson¹⁸ has recently shown.

In addition to the determination of urobilinogen in the urine, two other tests of hepatic function were employed—the bilirubin excretion test and the hippuric acid synthesis test. At least one of the three tests of hepatic function was performed in 63 of the 74 cases, and in 35 of the 63 cases (56 per cent) there was evidence of reduced hepatic function. The incidence is sufficiently high to suggest that a poorly functioning liver may be of etiologic significance in various types of blood dyscrasia. In 24 (71 per cent) of the 34 cases in which all three tests of hepatic function were performed, evidence of hepatic damage was shown by at least one test, the urobilinogen content of the urine was elevated in 10 of the 24 cases, the bilirubin test gave a positive reaction in 13 and the hippuric acid test gave a positive reaction in 16. In only 3 of the 34 cases did all three tests give positive results,

18 Watson, C. J. Studies on Urobilinogen. III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, *Arch. Int. Med.* **59**: 206-231 (Feb.) 1937.

but all three tests gave negative results in 10 of the 34 cases. These observations serve to emphasize the importance of carrying out several tests in each case before concluding that hepatic function is normal or abnormal. A single test showing a positive result is highly suggestive of hepatic damage, whereas a single test showing a negative result is of little significance. The possibility that anemia per se with hepatic ischemia is responsible for the impairment of hepatic function seems unlikely in view of the fact that in 7 of the 10 cases in which there was no evidence of hepatic damage by any of the three tests, pronounced anemia was present, with a hemoglobin level of 50 per cent or below.

Since the liver is recognized as the principal detoxifying organ of the body, the high incidence of hepatic damage in various forms of blood dyscrasia suggests that harmful substances inadequately detoxified by an ailing liver may damage the bone marrow and thereby give rise to peculiar refractory anemias or even leukemias.

SUMMARY AND CONCLUSIONS

The excretion of urobilinogen has been studied in 74 cases of blood disease. The average daily output of urobilinogen in the feces is regarded as an index of the rate at which erythrocytes are being destroyed in the body.

Abnormally high values for urobilinogen in the feces were obtained in the cases of hemolytic anemia and in most of the cases of pernicious anemia in relapse; these values returned to normal after splenectomy in the cases of congenital hemolytic jaundice and after adequate liver therapy in the cases of pernicious anemia.

Based on these observations, the conclusion is reached that destruction of blood is increased in pernicious anemia, even though the disease may not be primarily a hemolytic anemia.

The anemia occurring in association with leukemia is occasionally hemolytic. In rare cases of aplastic anemia a hemolytic factor is apparently active; splenectomy in 2 such cases was followed by temporary improvement.

Transfusion of well matched blood may at times be followed by a striking increase in the excretion of bile pigment, suggesting that the better part of the transfused blood is rapidly hemolyzed in such instances.

In 63 of the 74 cases of blood disease the hepatic function was studied by one or more of three tests: the test for urobilinogen in the urine, the bilirubin excretion test and the hippuric acid synthesis test. Evidence of hepatic dysfunction was obtained in over 50 per cent of the cases, suggesting that a disturbance in the function of the liver may play a significant role in the pathogenesis of many of the blood dyscrasias.

EXPERIMENTAL STREPTOCOCCIC ENDOCARDITIS

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AND

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ST LOUIS

I REPRODUCTION OF THE DISEASE BY MEANS OF INTRAVENOUSLY INJECTED STREPTOCOCCI

The fact that the treatment of bacterial endocarditis remains unsuccessful emphasizes the difficulty involved in understanding this disease. The utter failure to treat the disease successfully with such immunologic agents as serums and vaccines indicates also that the factors at work within the animal body are distinctive and for the most part unidentified. In a general way, two facts seem to be established by clinical studies: first, the patient who acquires bacterial endocarditis has invariably suffered previous injury to the tissues of the valves, and, second, bacterial endocarditis is established by the implantation in or on this injured valve of bacteria, usually nonhemolytic streptococci, which gain access to the blood stream through the medium of a local infection such as pharyngitis or otitis media. In some instances it is not known that previous injury to a valve existed. It is possible that an acute erosive injury to the valve received during an acute infection such as pneumonia may be followed promptly by implantation of bacteria. Recently reported studies of Nedzel¹ revealed the effect of intravenous injections of pitressin on the integrity of the endothelium of the mitral valve. Furthermore, it may be necessary to suppose that an old injury, rheumatic in origin, must be awakened by the intercurrent local infection in order for the valve to be susceptible to implantation. Again, there are certain instances in which the presence of an alleged intercurrent local infection cannot be discovered by physical examination or by study of the history and the route of infection remains undetermined. How the influence of exposure to cold operates is not clear, but such exposure may be the only feature of the history. The possibility of infection through the intestinal tract is by no means fanciful.

The mere recital of these features indicates how difficult it is even to state the question when approaching the discussion of this disease.

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¹ Nedzel, A. J. Experimental Endocarditis, *Arch. Path.* **24**: 143 (Aug) 1937.

The present report deals with an attempt to approach the problem, first, by reproducing the disease in dogs and then by studying the effect of experimental treatment

METHOD

Dogs weighing about 10 Kg each were used. These animals are sufficiently robust to tolerate the experimental conditions and possess carotid arteries large enough to admit the instrument used to injure the valves.

The instrument used is a plated rod, about 2 mm in diameter, which is tapered slightly and terminates at one end in a hook the inner border of which is beveled on both sides to give a cutting edge. The hook is compressed in its transverse diameter so as not to increase materially the width of the instrument at the point where it enters the artery. A suitable handle fits the other end of the rod. The length of the rod is about 18 inches (46 cm). These measurements are influenced by the length and the size of the lumen of the carotid artery.

The neck was shaved, and tincture of iodine was used to cover the site of operation, over the right carotid artery. After anesthesia was established with ether or amytal, an incision was made over the line of the right common carotid artery. Appropriate dissection exposed the carotid sheath. The artery was clearly isolated for 2 or 3 inches (5 to 8 cm) of its length, and two ligatures of linen were slipped beneath the artery. The distal ligature was tied. When the artery was lifted with the left index finger, the vessel could be compressed and a small cut could be made through the wall with a sharp scissors. Pressure by thumb and forefinger stopped the loss of blood, and the hooked end of the instrument was inserted through the cut and the rod was slid down into the aortic orifice of the heart. With practice it was possible to acquire the ability of perforating an aortic cusp. When the instrument was withdrawn, the cutting edge of the hook severed the cusp. If the aortic valve was not engaged, it was easy to hook the edges of the nearby mitral leaflet. The establishment of suitable injury was determined by the production of a loud murmur that persisted after the hook was withdrawn into the carotid artery. The proximal ligature was then tied, and the wound was closed.

Infection of the injured valve was attempted by the inoculation intravenously of a twenty-four hour plain broth culture of nonhemolytic streptococci of little or no virulence for white mice. It was considered important to wait at least thirty days after the operation before injecting these bacteria.

Culture of the blood was made by drawing blood from the left jugular vein. Agar was considered to be the best medium, since it permits the more definite identification of contaminating bacteria. Measured amounts of blood were used in order to determine the number of colonies. In case of doubt, the identity of colonies in relation to the strain injected was established by comparing fermentation reactions in the usual mediums containing carbohydrates.

RESULTS

In a previous report² the production of streptococcic endocarditis was described. At the time of that report the animals studied lived from twelve to eighteen days after infection of the injured valve. The period was too short for the study of therapeutic agents, even though

2 Kinsella, R. A. *Proc Soc Exper Biol & Med* 20 252, 1923

all the salient features of the disease in human beings were reproduced. Also, the conditions of the experimental infection were too severe to permit measured study. The chief modifications in procedure which led to more favorable results were the employment of streptococci of low virulence and the infection of the animals after allowing at least thirty days to elapse after the operation. With our present method, healthy dogs will tolerate the operation, remain in good condition until infected and then withstand the experimental disease for twenty-five days. Occasionally an animal lives for more than thirty-five days. Successful implantation of the cultures is determined by obtaining positive results of blood culture repeatedly.

Abortive Infection—This has occurred not infrequently, as demonstrated by the recovery of streptococci in small numbers, viz., two to five colonies per cubic centimeter of blood, followed by repeatedly sterile cultures with the animal remaining healthy. This curious occurrence may have its representation in human beings with acute rheumatic endocarditis for whom one or more positive results of blood culture are obtained without the establishment of bacterial endocarditis. Whether or not in such cases there are colonies of bacteria implanted on the surfaces of the injured valves without the production of underlying reaction was not determined except for those dogs which were treated by the method to be described later in this paper, nor was it possible to determine why such transitory bacteremia occurs without complete development of bacterial endocarditis. The animals in such cases are not as definitely sick as they are when the bacteremia becomes continuous, nor do they display the peripheral embolic effects of the fully developed infection.

Death Rate—No animal was ever found to have recovered from the definitely established infection of a cardiac valve. Eighty-seven dogs were studied in which increasingly severe illness characterized by embolic episodes attended the continuous bacteremia.

Bacteremia—Figure 1 presents the curve for colony counts in typical fatal bacteremia. The bacteremia was uniformly of the increasing type, the colonies beginning in low concentration and ending in countless numbers. The shorter the duration of life, the more acute the angle of ascent of the curve representing the colony counts. This is unlike the appearance of the chart in cases of bacteremia in human beings. In the latter case the colony count is maintained at a uniform level, either high or low, throughout life.

Suppressed Bacteremia—It seems likely that whatever factor controls the bacteremia, keeping the number of colonies per cubic centimeter of blood at a constant level, is associated with protection. In order to inquire into the question of whether or not immunization to streptococci is responsible for control of bacteremia, experiments were carried out.

A In the first series of these experiments, 6 animals were inoculated two weeks after valvotomy with cultures of living streptococci, previously exposed for thirty minutes at 37 C to the action of serum of dogs that had died of the infection. This serum caused the organisms to become agglutinated. Four of these 6 animals displayed a tendency to constancy of the colony count (figure 2 illustrates this result). As other animals at a later date, surviving for thirty to thirty-

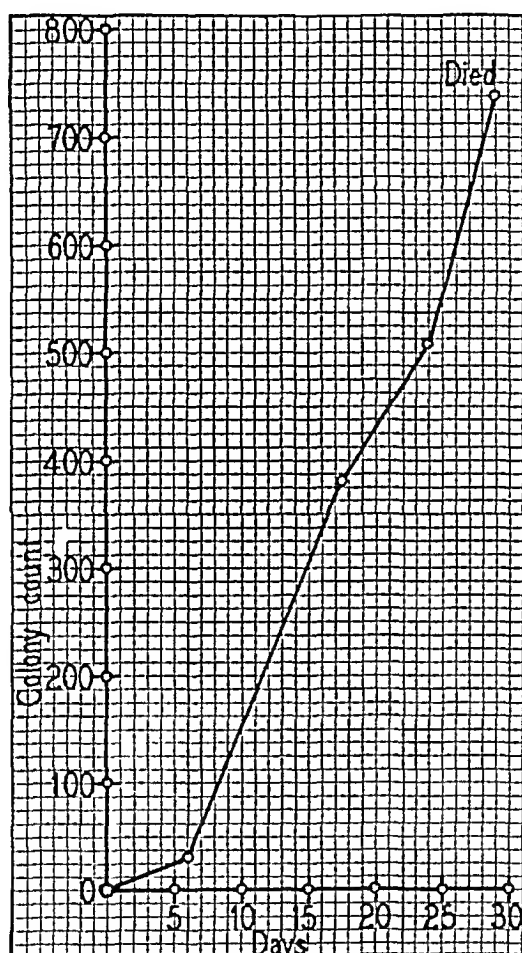


Fig 1—Bacteremia in a dog that had not been treated. The colony count indicates the number of colonies per cubic centimeter of blood.

five days, also displayed this tendency without being infected by such agglutinated bacteria, it is unsafe to conclude that the agglutinins so injected conveyed any influence responsible for the suppressed bacteremia.

B In a second series of experiments, 2 dogs previously injured by valvotomy received intravenous injections of killed cultures of non-hemolytic streptococci every four days until five such injections had

been made. At this time the serum of both animals gave strong agglutination reactions with the cultures used for injection. Subsequent injections of living cultures produced the usual fatal disease.

C. In a third series of experiments, 4 animals previously injured by valvotomy received injections of living hemolytic streptococci in one knee joint. Although local inflammatory reaction developed, culture of the blood remained sterile in each instance for ten days. One animal was killed and showed a traumatized cardiac valve without infection. The other 3 animals were successfully infected by intravenous injection and at autopsy displayed typical bacterial vegetation.

Pathologic Features—The accompanying photographs illustrate effectively the complete similarity between the experimental infection and the disease in human beings.

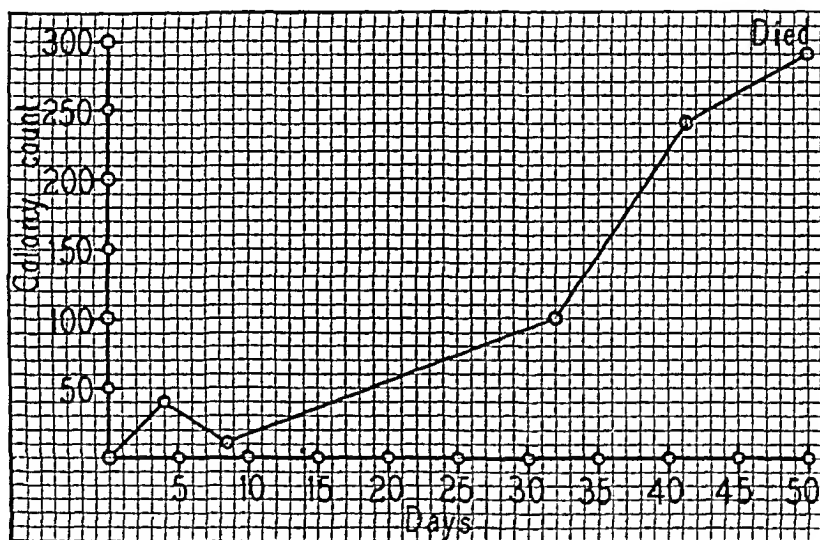


Fig. 2—Bacteremia produced by the use of agglutinated organisms

The vegetations (fig. 3) were of varying sizes and showed a capacity to spread infection by contact. Thus a vegetation originating on an injury of one of the aortic cusps would apparently cause a vegetation to develop on the nearby leaflet of the mitral valve. Even when no gross evidence of vegetation could be seen, inspection of the tissue under the microscope revealed spreading bacterial growth along the surface of the valve, onto the auricular surfaces and along the surfaces of the chordae tendineae, often without any underlying cellular response.

Microscopically (fig. 4) the vegetation consisted of dense masses of bacteria, loosely held in a matrix of pink-staining material, with rich leukocytic infiltration of the underlying valvular structures.

Typical embolic localizations occurred in the kidney and spleen. Cerebral infarction was not infrequent. More interesting were the

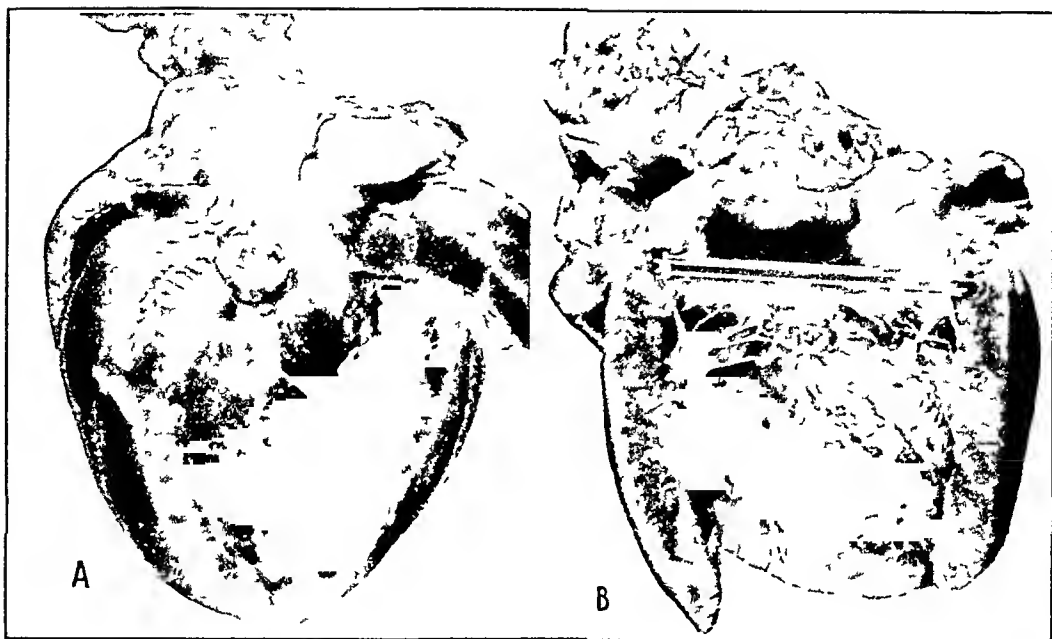


Fig 3—*A* shows vegetation on the aortic cusp, *B* shows vegetation on the mitral valve

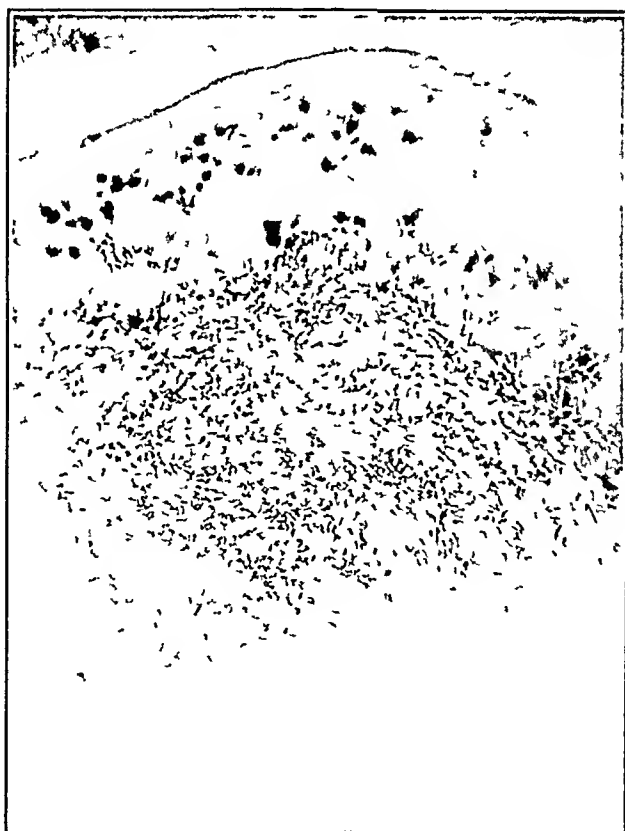


Fig 4—Microscopic study of the vegetation on the mitral valve, showing colonies in a pink-staining matrix, with an underlying zone of neutrophils and lymphocytes

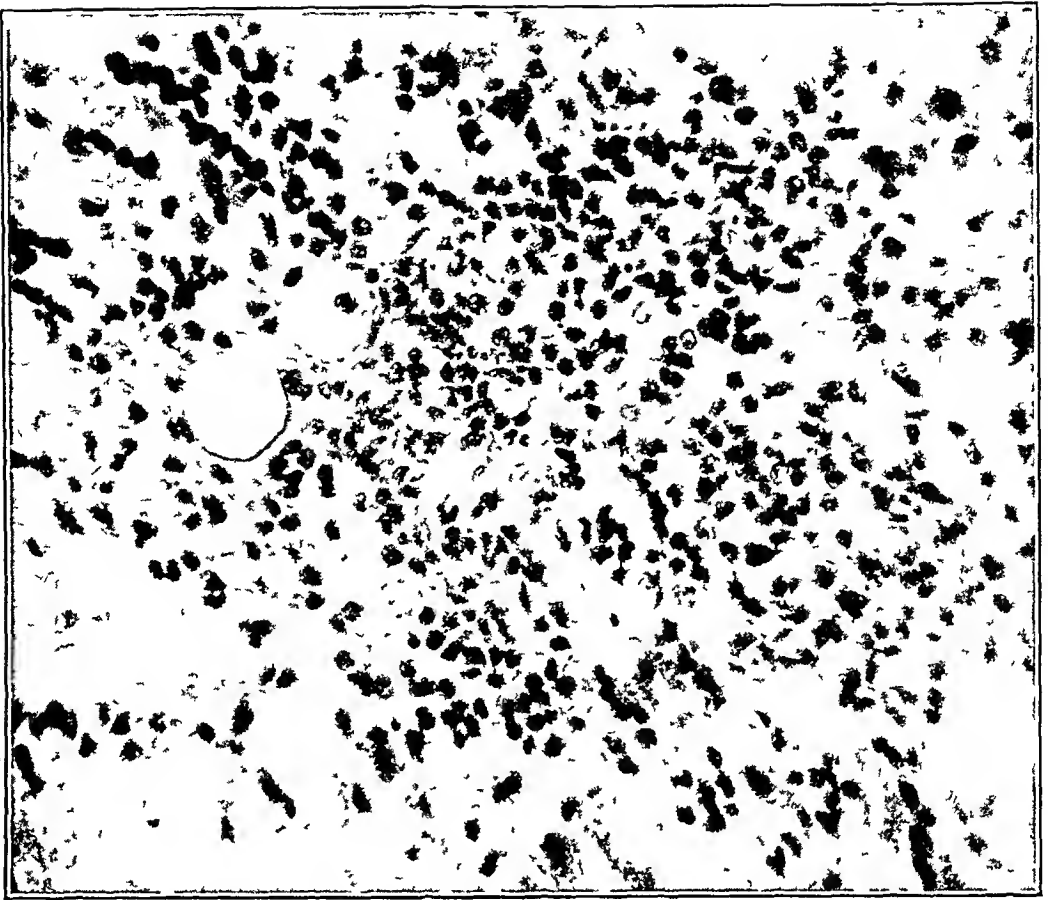


Fig 5—Photomicrograph showing punctate hemorrhage in the cardiac muscle at the stage when infiltration with neutrophils and lymphocytes had begun

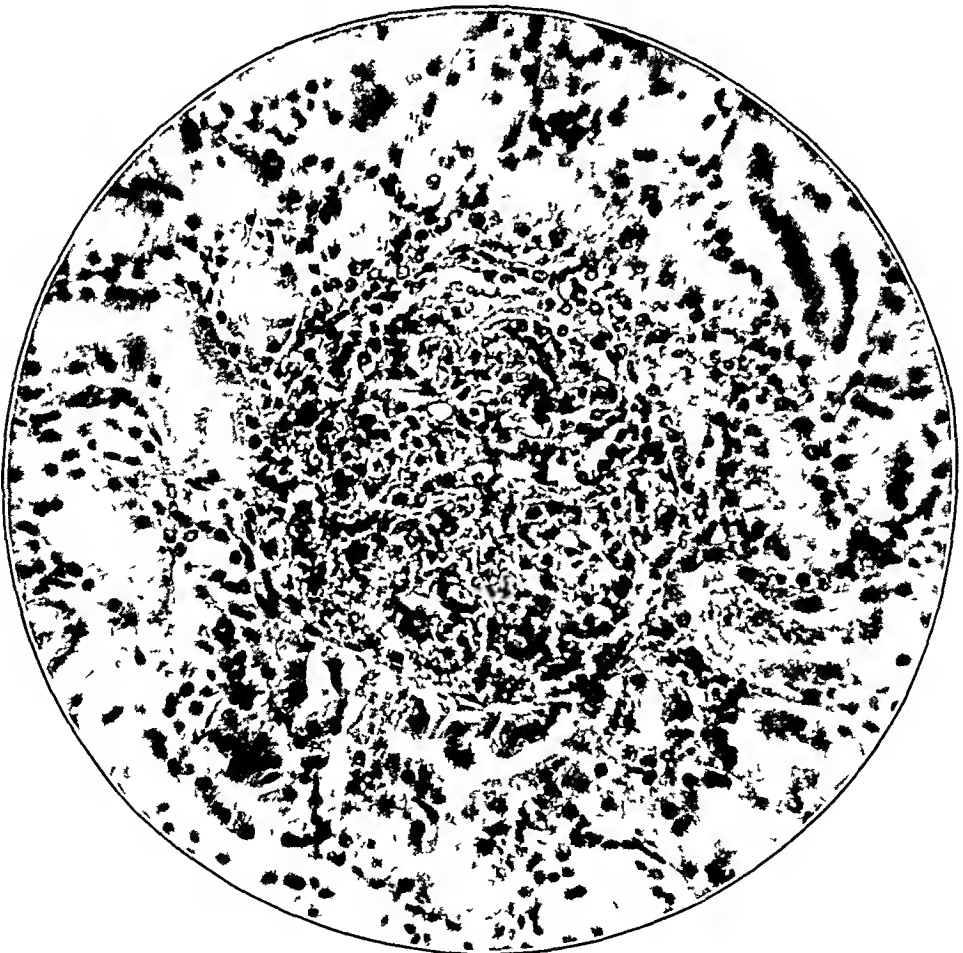


Fig 6—Hemorrhage into the glomerular tuft, with beginning exudation of neutrophils and lymphocytes

minute vascular lesions which were present in the brain, heart (fig 5), skeletal muscles and glomeruli (fig 6). These lesions seemed to begin as punctate hemorrhages which became infiltrated with leukocytes and finally with small round cells. The animals did not show any later development of the lesions. These lesions could easily account for the disturbances sometimes manifest in the electrocardiogram, probably for the mental changes in human beings, for the appearance of red and white blood cells in the urine, for the petechiae which appeared in the conjunctiva and in the skin of some of the animals and for the spotted appearance of the surface of the kidneys (fig 7). These lesions have



Fig 7—Photograph showing the typical "flea-bitten" kidney

often been assumed to be of embolic formation. Serial sections made through a petechial lesion in the skin failed to throw light on their mode of formation.

COMMENT

Bacterial endocarditis can be produced in dogs by the methods described. This disease in dogs presents features identical with those observed in the disease in human beings. The difference in the bacteremia is quantitative and no doubt depends on the absence of those factors which make the duration of the disease in human beings more prolonged. Of particular interest are the lesions in the kidneys—the glomerular thromboses (fig 8), so characteristic of the disease in human beings. The fatal character is invariable in dogs—as it seems to be in

human beings. Variations occur, implantation of bacteria being defeated either because of failure of the bacteria themselves to gain a foothold or because of some indifference on the part of the tissues. The evidence obtained does not support the idea that animals can be immunized either by intravenous inoculation of killed streptococci or by the establishment of a local infection. Nor were we able to bring about infection of the injured valve through the medium of such a local infection.

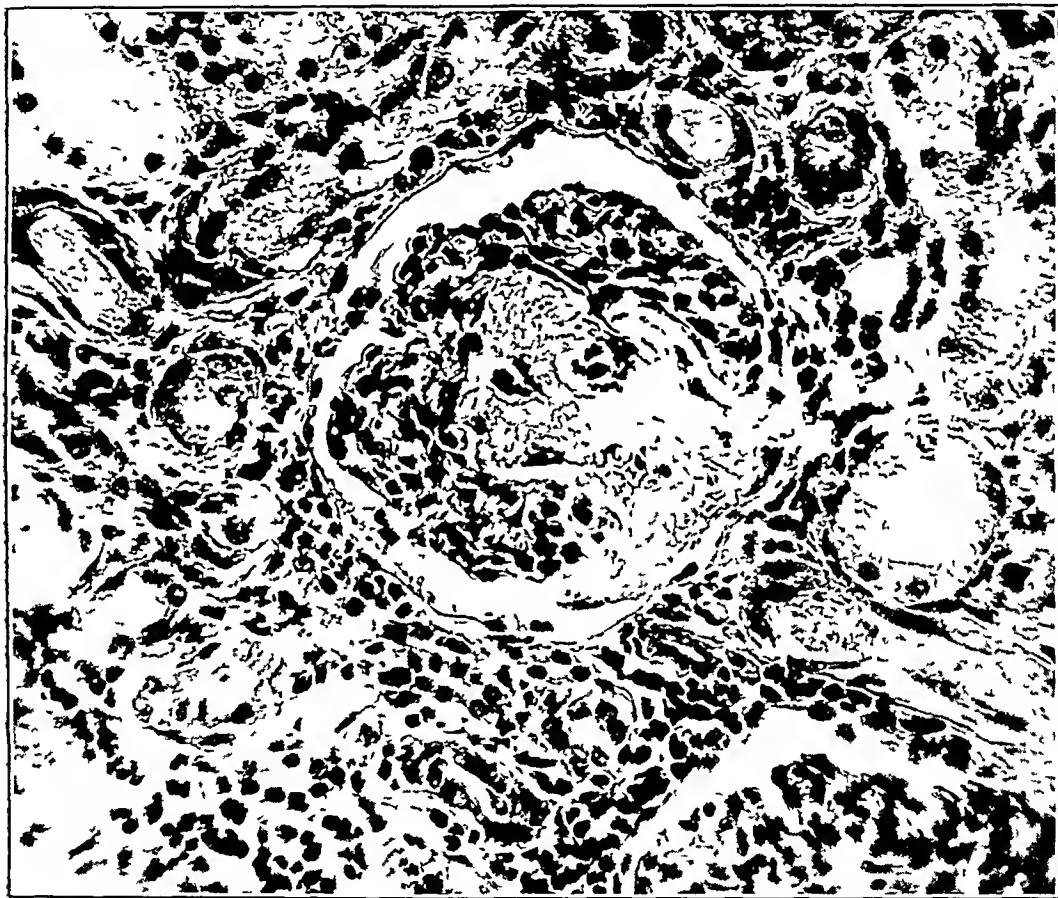


Fig 8—Photomicrograph showing thrombosis of part of a glomerular tuft

The assumption is invited that infection of the valve in human beings, if it does occur through the medium of local infection, is further encouraged by changes going on in the injured valve itself which make implantation possible. According to this reasoning, an old rheumatic lesion of the valve does not become converted into bacterial endocarditis with any and every intercurrent bacteremia which may occur during the life of the individual but requires some change in its own economy to bring about such a disaster.

II TREATMENT OF THE DISEASE

Many attempts have been made to effect a cure in patients suffering from bacterial endocarditis. Perhaps the literature does not contain a description of the most bizarre of these attempts. Serums, variously produced, and vaccines are some of the agents employed. These agents are so uniformly unsuccessful that the inference might be drawn that the immunologic approach to treatment cannot succeed.

This part of our report deals with the study of the effect of treating the experimental disease by intravenous injection of an organic mercurial drug (merthiolate) and by oral administration of sulfanilamide.

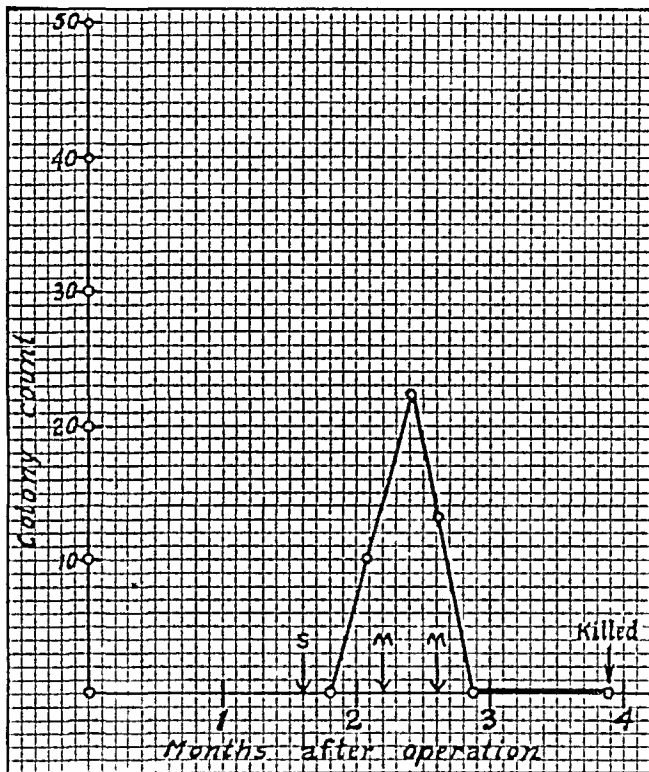


Fig 9—Bacteremia lasting for eighty-six days. In charts 3 to 7, S indicates intravenous injection of 10 cc of a culture of streptococci, M, injection of 10 cc of 1 per cent solution of merthiolate.

TREATMENT WITH MERTHIOLATE

Method—Animals were prepared by the method previously described. Care was taken to select dogs weighing from 10 to 12 Kg. One month was allowed to elapse after the operation before streptococci were injected intravenously. When the resulting cultures yielded only a few colonies per cubic centimeter of blood, several positive results of blood culture were obtained before merthiolate was injected. In this way the possibility of an "abortive infection" was excluded. When bacteremia was established, with a high colony count, merthiolate was used without waiting for further positive results of blood culture.

Buffered merthiolate was used in most instances in a dosage of 1 cc of 1:100 dilution to each kilogram of body weight of the dog. When a dilution of 1:1,000 was used, less effect was noted. The diluent was isotonic buffered salt solution.

For this part of the study there were 14 animals from which acceptable evidence could be obtained. Other animals were excluded on account of accidents which interfered with the experiment.

Clinical Results—During the attempts to treat animals with merthiolate, it was found to be especially true that strains of streptococci differ in their capacity to produce bacteremia. Thus the strain which was called CH immediately produced infection, with counts of over

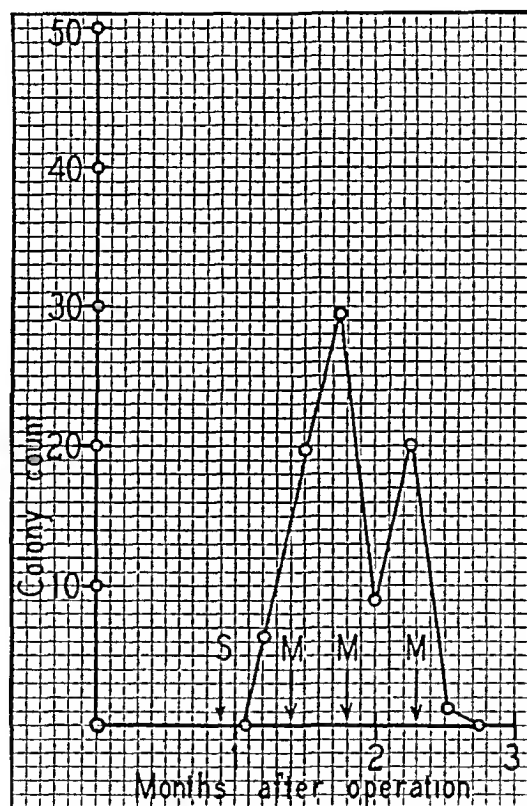


Fig. 10—Bacteremia lasting for seventy-five days. This animal was killed eight and one-third months after operation. Culture of the blood at autopsy was sterile.

1,000 colonies per cubic centimeter of blood. Against this type of bacteremia, merthiolate was scarcely effective, producing only slight reductions in the colony count. There were 5 animals in this group.

A strain called G, which was unfortunately lost after a short time, produced a type of bacteremia characterized by a small number of colonies per cubic centimeter of blood. This type of infection yielded readily to intravenous injections of merthiolate. There were only 2 animals in this group, and both were apparently completely cured (figs. 9 and 10). One of these animals was killed forty-four days

after being infected and twenty-three days after the last positive result of blood culture. The other animal was allowed to live for eight months after the last positive result of blood culture.

Seven of the animals studied were given intravenous injections of cultures of a strain of streptococci called WK. This strain seemed to stand midway between G and CH as to virulence for dogs and produced a type of bacteremia which rapidly increased in severity and tended to recur even after successful sterilization with merthiolate.

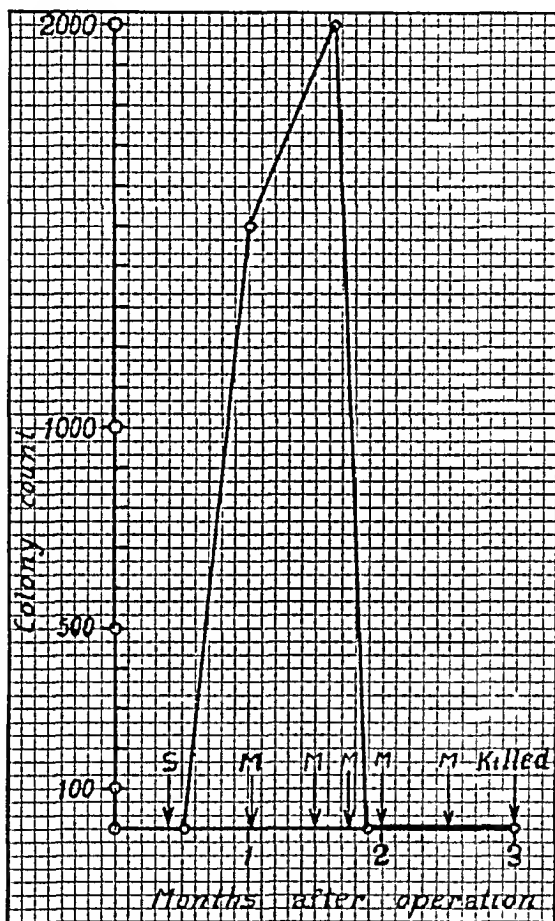


Fig 11—Bacteremia lasting for thirty days. The animal was killed after three months, culture of the blood was sterile.

Three animals in this series (figs 11 and 12) were apparently cured. In 1 of these animals (fig 11) bacterial masses were seen microscopically on the surface of the valve, without underlying cellular response (fig 13). Although cultures of the heart blood made at autopsy were sterile, the tissue of the valve was not ground for culture. It is therefore impossible to state whether the bacteria were viable. This interesting observation will be discussed later.

In 1 case (fig 14) there was an apparent cure, although the animal died of pneumonia before observations were completed. This animal likewise displayed bacterial masses without underlying reaction (fig 4).

One animal (fig 15) was treated without cure but with prolongation of life and with a definite effect on the severity of the bacteremia. The

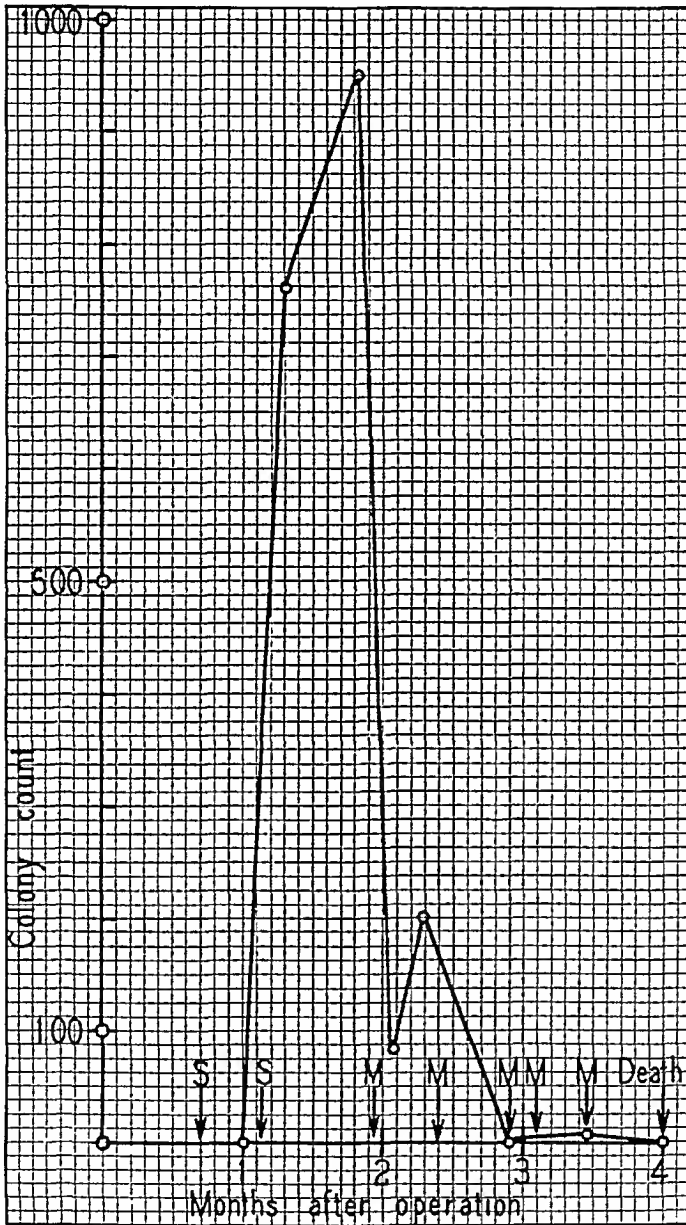


Fig 12—Bacteremia lasting for seventy-three days. At autopsy, culture of the blood was sterile.

apparent explanation of the failure of the drug in this case is to be found in the fact that insufficient amounts of merthiolate were employed.

The last 2 animals in this series which were given injections of strain WK were incompletely observed because death intervened (in

1 case due to cerebral infarction and in the other to pneumonia) before the effects of merthiolate (already favorable) could be established

Of the 9 animals given injections of strains G and WK, 5 were clinically cured, 2 showed remarkable improvement and 2 were incompletely observed because of early death

Effect of Successful Treatment on Reaction of the Tissues of the Valves—As has already been shown (fig 3), the disease established on the injured valve presents gross and microscopic features identical with those observed in human beings. The vegetations consist of



Fig 13—Photomicrograph showing the remains (?) of heavy bacterial vegetation in a cured animal. Note the absence of signs of underlying reaction in the tissue of the valve.

masses of bacteria encrusted on the surface of the valve and neighboring endocardium. Immediately underneath these bacterial masses is a dense infiltration of leukocytes, occupying most of the thickness of the valve. In the cases of 2 animals (figs 9 and 12), both of which had apparently recovered from infection and which yielded sterile blood culture at autopsy, masses of bacteria, perhaps dead, occupied the surface of the valve, but there was no underlying reaction in the tissues. It is unfortunate that such valves were not ground and cultures made

to determine the viability of the bacteria in question. It can probably be assumed that these bacteria were not viable. That they did not break away from the surface of the valve and cause embolic effects seems remarkable. Analogy is suggested with the condition of the valves observed in some cases of acute rheumatic fever in human beings recently discussed by Von Glahn and Pappenheimer³. These patients showed transiently positive results of blood culture and at autopsy the

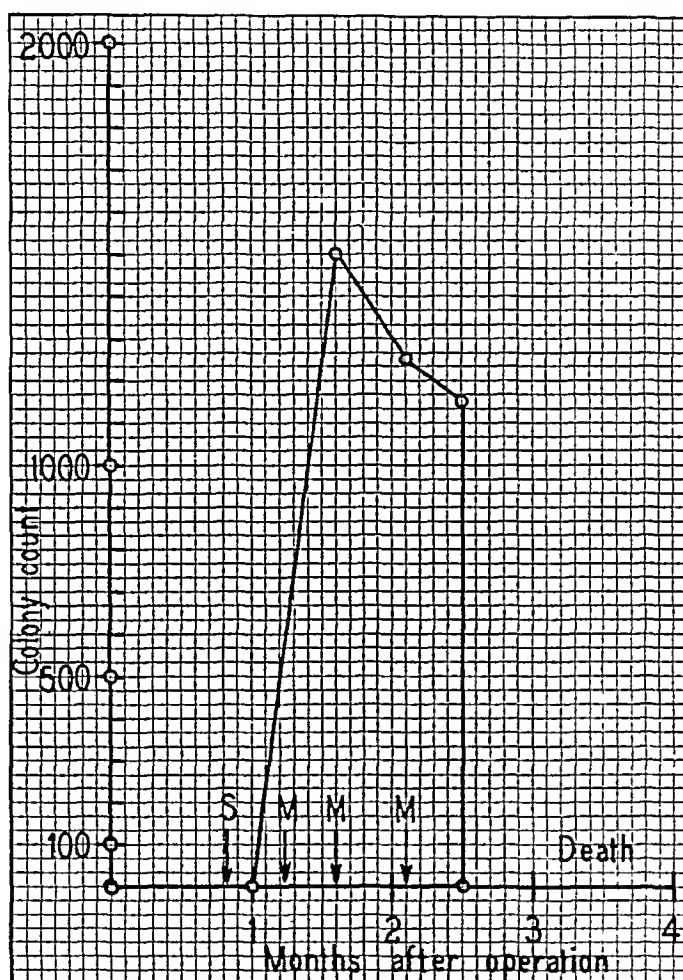


Fig 14—Bacteremia lasting for thirty-two days. At autopsy the culture of the blood was sterile.

valves were studded with microscopic colonies of streptococci, without underlying reaction in the tissues. The evidence presented by the study of experimental bacterial endocarditis in dogs suggests no relation between acute rheumatic fever and bacterial endocarditis. As a matter of fact, the two diseases are never seen in human beings simultaneously. The

3 Von Glahn, W. C., and Pappenheimer, A. M. Relationship Between Rheumatic and Subacute Bacterial Endocarditis, *Arch Int Med* **55** 173 (Feb) 1935.

question is left open as to whether merthiolate kills the bacteria directly or renders the tissues underlying the implanted masses impervious or indifferent

Appearance of the Healed Valve—In those animals which were cured and which came to autopsy between six and eleven months after sterile culture of the blood was obtained continuously, the microscopic appearance was that of glistening verrucae, coarser than those seen in

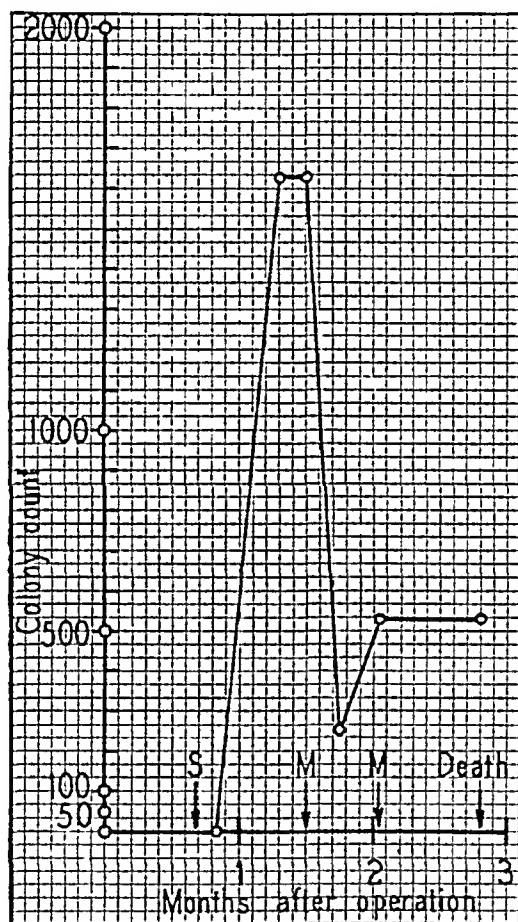


Fig 15—Bacteremia lasting for thirty-nine days S indicates injection of 10 cc of a culture of streptococci The first injection of merthiolate (1 1,000), M, consisted of 1 cc , the second, of 2 cc

human beings with old rheumatic disease Microscopically (fig 16 A) there was a granulomatous arrangement, with frequent large but not definitely polynuclear cells—a picture sometimes, but most probably incorrectly, likened to that of Aschoff bodies A comparison of such a picture with that of the valve which has been injured and has healed without infection (fig 16 B) is interesting

It seems to be logical to compare the healed infected valve with the healed rheumatic valve of a human being. Further studies are projected in which such animals will be reinfected and a repetition of the therapeutic attempts will be carried out.



Fig 16—*A*, cross section of a valve that had healed after the infection; *B*, cross section of a valve that had healed after trauma without infection

The failure of methiolate and sulfanilamide to be useful in the treatment of human beings with streptococcic endocarditis and their success in the treatment of dogs may depend on the rather fundamental difference between the infected traumatized valve in the dog and the infected diseased valve in the human being.

TREATMENT WITH SULFANILAMIDE

The successful treatment of streptococcic infections with sulfanilamide (para-aminobenzenesulfonamide) by Long and Bliss⁴ in this country, after the investigations of Domagk⁵ and others in Europe, has given emphasis to the study of chemotherapy in infectious diseases. We have had success in the treatment of experimental endocarditis with merthiolate. We have not, however, been able to apply this therapy successfully to endocarditis in human beings and therefore have continued to search for a more satisfactory drug. Sulfanilamide was chosen for further investigation since its applicability to human beings was already proved. Furthermore, it was deemed wise to note the effects of the drug in the experimental animal before giving it to the patient suffering from subacute bacterial endocarditis.

Method—Five dogs weighing 10 Kg each were anesthetized by the administration of a barbiturate into a vein. The carotid artery was exposed, and the hooked instrument was passed down into the heart. An attempt was made to injure a valvular leaflet, if a murmur persisted after withdrawal of the instrument, success was indicated.

All the animals had persisting murmurs after recovery from the operation. About two weeks after the operation each dog except dog 137 was given 10 cc of a culture of *Streptococcus viridans* intravenously. Dog 137 was fed *Str viridans* for thirty-three days before the organisms were given intravenously. Blood was taken daily for culture, and when culture gave positive results on three successive days the use of the drug was started. Two dogs (dogs 237 and 937) failed to yield a positive result of culture and required a second injection.

Once the infection was established, treatment with sulfanilamide was started. The dose was arbitrarily set at 20 grams (13 Gm) per day, and each dog received the daily dose through a stomach tube. Blood was taken for culture every two or three days, and treatment with the drug was continued until the dog had been free from bacteria for from three to five days. Once the use of the drug was stopped, culture of the blood was repeated at less frequent intervals. In one instance (dog 937) treatment was continued for thirty-eight days because the results of culture remained positive. The dog finally died, apparently of the infection.

Results—The five dogs gave negative results of blood culture five and ten days after operation. Each dog showed a positive result after intravenous injection of living streptococci, 2 dogs required a second injection. Once a positive result of culture was obtained, the bacteria were constantly present, usually in increasing numbers, until therapy was introduced.

4 Long, P. H., and Bliss, E. A. Para-Amino-Benzene-Sulfonamide and Its Derivatives. Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcic Infection, Preliminary Report, J. A. M. A **108** 32 (Jan 2) 1937.

5 Domagk, G. Klin. Wchnschr **15** 1585 (Oct 31) 1936.

Twenty grains (1.3 Gm.) of sulfanilamide given daily successfully freed the blood stream of 4 dogs of bacteria. One dog died despite treatment, although the course of the septicemia was prolonged to thirty-eight days (fig. 3A).

The drug in the doses employed did not seem to be toxic for any dog. The 4 survivors were well after periods ranging from three to six months.

The examination of the tissues of dog 937 showed evidence of severe septicemia. Sulfanilamide could not be held responsible for this death.

Conclusion—On the basis of our work we must conclude that sulfanilamide in the doses used is an effective agent for freeing the blood stream of *Str. viridans*.

Four dogs were cured of persistent septicemia with *Str. viridans* by the administration of sulfanilamide. One dog succumbed to the infection, although the drug was administered in the usual way.

III. REPRODUCTION OF THE DISEASE BY MEANS OF ORALLY ADMINISTERED STREPTOCOCCI

The production of an infectious disease by the oral administration of bacteria has been accomplished in the case of typhoid by Metchnikoff and Bezredka.⁶ One may be critical of the similarity which this experimentally produced infection bears to what might be called the typical clinical picture of typhoid. A review of the literature does not reveal any other work in which a clinical infection as seen in man has been reproduced in animals by the feeding of the etiologic agent.

On the other hand, numerous workers have reported successful immunization of animals by feeding living and killed bacteria. Most of this work has been carried out with typhoid and paratyphoid and dysentery bacilli.

During our study of streptococcic endocarditis produced by injuring the cardiac valves of dogs with subsequent intravenous inoculation with streptococci, an attempt was made to study the possibility of protecting animals after injury of the valves by feeding killed and living streptococci. While a number of such animals were unaffected by the feeding and later became infected by intravenous inoculation, several animals became sick before intravenous inoculation, and at autopsy were observed to have vegetative lesions on the injured valves. On microscopic examination these vegetations were seen to be composed of streptococci.

⁶ Metchnikoff, I., and Bezredka, A. *Terap. Obozr.* 4: 161, 1911, *Ann. Inst. Pasteur* 25: 193, 1911.

After this fortuitous result, a deliberate attempt was made to study the possibility of infecting injured cardiac valves by feeding streptococci

METHODS

Animals were selected which weighed about 10 Kg and were free from infection after a suitable period of isolation. The operation was performed with the animal under amytal narcosis. Usually it resulted in cutting the cords of the mitral valve. This injury had proved sufficient for the implantation of subsequently injected bacteria.

For the first series of animals, 10 cc of pure twenty-four hour plain broth culture was mixed with food and presented to the animals. For the second series of animals the culture was administered through a small stomach tube.

TABLE 1 (*Group 1*)—*Positive Results*

Dog	Operation	Feeding	First Positive Blood Culture	Death
4a	11/23/25	11/27	12/ 2	12/ 4
7	12/17/35	12/18	12/24	12/29
9	12/17/35	12/18	12/24	12/26
1	12/ 4/35	12/ 6	12/ 9	1/21
15	4/ 1/35	4/ 2	4/11	4/12
22	3/24/35	4/ 6	4/ 9	4/10

TABLE 2 (*Group 1*)—*Negative Results*

Dog	Operation	Feeding	Feeding Stopped	Number of Blood Cultures	Intra-venous Inoculation	First Positive Blood Culture	Death
13	1/13/36	1/14	2/25	10	2/25	2/29	3/ 1
12	1/ 8/36	1/10	2/12	8	2/12	2/16	2/19
14	1/20/36	1/21	2/12	5	2/12	2/19	
10	12/30/35	1/ 1	1/ 7	3	1/ 7	1/13	
6	12/25/35	12/26	1/ 3	5	1/ 3	1/ 9	3/16

Blood culture was made every three or four days during the experiment. When vegetations were observed at autopsy, the bacteria of the vegetations as well as the bacteria found in blood cultures were studied to determine their identity. To study the identity, the agglutinability of the recovered bacteria with anti-serum homologous with that of the injected bacteria was tested. Also the fermentation reactions were compared, inulin, sucrose, mannitol and lactose being used as test substances.

RESULTS

In the first series of dogs, which were given the streptococci in broth culture mixed with the food, there were 11 animals. Tables 1 and 2 show the interval between the operation and the date of the beginning of feeding with streptococci. Six animals became infected, as shown by positive results of blood culture, and 5 animals, although fed as soon after the operation as the others, did not become infected. After

from three to ten sterile cultures were obtained, these animals were inoculated intravenously with streptococci, and endocarditis developed. This last fact indicates that the injury to the valve in these animals was sufficient to permit the implantation of bacteria.

In those dogs which became infected promptly after the feeding with streptococci was begun, the infection was of the fulminating type, such as is seen in animals inoculated intravenously within the week after injury of the valves.

In those dogs which did not become infected by the feeding, no immunity was developed by the feeding. In the case of dogs 12 and 13, the intravenous injection of streptococci occurred thirty-five and forty-three days, respectively, after the operative injury. This should have led to the more prolonged disease, according to extensive previous

TABLE 3 (*Group 2*)—*Positive Results*

Dog	Operation	Feeding	First Positive Culture	Result
137	2/ 2/37	2/ 4	2/ 6	2/ 9 Death
937	3/25/37	3/26	3/31	4/15 Treatment
737	3/25/37	3/26	3/31	4/15 Treatment
837	3/25/37	3/26	4/ 2	4/16 Treatment

TABLE 4 (*Group 2*)—*Negative Results*

Dog	Operation	Feeding	Feeding Stopped	Bacteria Injected	First Positive Culture	Result
337	2/5/37	2/6	2/22	2/26	3/1	3/8 Death
237	2/2/37	2/4	2/16	2/17	3/1	3/5 Treatment

experience. However, it will be seen that all the dogs in this group lived only a short period (four, four, seven, six, six days, respectively). In the case of dogs 12 and 13, it is suggested that the endocarditis may have existed before the intravenous inoculation was made, thus adding to the number of animals infected by feeding.

In the second series of animals the culture of streptococci was put in the stomach through a small stomach tube. Four of the 6 animals in this series became infected, as revealed by repeatedly positive results of blood culture. The 2 animals which showed sterile blood cultures after what seemed an adequate period of feeding were then inoculated intravenously with streptococci and on being infected were utilized for the study of the treatment with drugs.

Tables 3 and 4 show the results in this series.

Bacteriology—The strains of streptococci obtained by culture of the blood and by culture of the vegetations removed at autopsy were com-

TABLE 5 (*Group 1*)—*Sugar Reactions**

Sugars	Dog from Which Bacteria Were Obtained							
	4a	4	10	6	9	7	8743	8911
Mannitol	—	1	A	A	A	A	A	A
Lactose	1	A	A	A	1	A	A	A
Sucrose	1	A	1	A	A	A	A	A
Melitose	—	—	—	—	—	—	—	—
Inulin	—	—	—	—	—	—	—	—
Saline	1	A	A	A	A	Slight A	A	A

* The sugar reactions were read at the end of 48 hours, at which time they had become constant. A indicates acid reaction. Bacteria obtained from a patient were used in this experiment.

TABLE 6—*Agglutination Test*

Dilution	Dog from Which Bacteria Were Obtained							
	4a	4	10	6	9	7	8743	8911
1 10	1+	1+	4+	4+	4+	4+	4+	4+
1 40	4+	4+	1+	4+	1+	4+	1+	4+
1 80	4+	1+	4+	4+	4+	4+	4+	4+
1 160	4+	4+	4+	1+	4+	4+	4+	4+
1 320	1+	4+	4+	4+	4+	4+	4+	4+
1 640	1+	4+	4+	4+	1+	4+	4+	4+
1 1,280	4+	4+	1+	4+	4+	4+	4+	4+
Control serum	—	—	—	—	—	—	—	—
Organisms	—	—	—	—	—	—	—	—

TABLE 7 (*Group 2*)—*Fermentation Tests*

Sugars	Dog				
	2B37	8B37	7B37	9B37	Control
Mannitol	A	1	A	A	A
Lactose	A	1	1	A	A
Sucrose	1	1	1	A	A
Melitose	—	—	—	—	—
Inulin	—	—	—	—	—
Saline	Slight A	1	1	Slight 1	A

* The cultures were read after forty eight hours.

TABLE 8 (*Group 2*)—*Agglutination Reaction*

Dilution	Dog			
	2B37	8B37	7B37	9B37
1 10	4+	4+	4+	4+
1 40	4+	1+	4+	4+
1 80	4+	4+	4+	4+
1 160	4+	4+	4+	4+
1 320	4+	4+	4+	4+
1 640	4+	3+	4+	4+
1 1,280	4+	3+	3+	4+
Normal serum	0	0	0	0
Control organism	0	0	0	0

pared with the strain used in the feeding. Tables 5 to 8 show the complete identity of these strains as regards both agglutinability and fermentation reactions.

Pathologic Data—Grossly the vegetations on the mitral valve and along the injured chordae tendineae were poorly developed though definite. They did not attain the size of vegetations usually seen in animals inoculated intravenously thirty days or more after operative injury. They were like the vegetations seen in animals inoculated intravenously a few days after such injury. In other words, since the endocarditis was of short duration, the vegetations were not large. Besides the endocardial lesions, infarcts of typical variety were present in the spleen, kidney and elsewhere. Microscopically the vegetations were composed of masses of streptococci.

SUMMARY

Seventeen dogs were subjected to operation whereby the mitral valve or the chordae tendineae were cut. All these animals were then fed with living cultures of nonhemolytic streptococci either mixed with food or by stomach tube. Ten of the animals became sick, displayed positive results of blood culture and died. At autopsy these infected animals had bacterial endocarditis. The bacteria in the vegetations were determined to be identical with those that had been fed to the animals.

CONCLUSIONS

Streptococcic endocarditis can be produced in dogs with injured cardiac valves by feeding them streptococci.

The fact is thus established that bacteria entering the animal body through the mouth may become implanted on an injured area within the body. The exact route which these bacteria follow is not determined.

GENERAL SUMMARY

The reproduction of streptococcic endocarditis is complete. The success of two different drugs in curing the disease in dogs, while failing to cure the disease in human beings, does not obscure the identity of the experimental disease. On the other hand, the difference in the mode of production of the experimental disease and in the mode of production of the disease in human beings is emphasized. This difference lies in the fact that bacterial implantation begins after an injury produced by trauma in the one instance and as a result of disease in the other. It seems highly important to collect a series of animals cured of streptococcic endocarditis and then to study the treatment after reinfection of the healed scars of previous infection. This will be a tedious

task The most interesting by-product of the present study has been the demonstration of infection of traumatized valves by means of feeding streptococci to the animal This part of the work, repeated in different years, seems adequately authenticated It is of further interest that none of the microscopic appearances in the heart or elsewhere was such as to suggest a relation between the lesions observed in dogs and those of rheumatic fever which appear in human tissues

LESIONS OF PERIPHERAL NERVES IN THROMBOANGIITIS OBLITERANS

A CLINICOPATHOLOGIC STUDY

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The most important manifestation of thromboangitis obliterans is pain. To the physician its severity and persistence may present a problem that exhausts his ingenuity. To the patient it may mean not only great suffering but also incapacity for work, sleepless nights, anorexia, loss of weight, mental breakdown and finally loss of a limb. In the majority of cases in which amputation of a limb is required in thromboangitis, it is done not because of extensive gangrene, ascending infection or septicemia but because of pain—severe, prolonged, uncontrollable, unbearable pain. Furthermore, the great majority of patients who have this disease are not “neurotic” or hypersensitive, their tolerance for pain is somewhat above the average.

Goldsmith and Brown¹ have analyzed the types of pain in thromboangitis obliterans and have grouped them under the following headings: (1) vascular inflammatory pain, (2) pain of acute arterial occlusion, (3) intermittent claudication, (4) pretrophic pain, (5) pain of ulceration and gangrene and (6) ischemic neuritis. In the final analysis all pain in thromboangitis obliterans must be produced by irritation, inflammation or degeneration of either sensory nerve endings or peripheral nerve trunks. However, pathologic studies of the peripheral nerves in thromboangitis obliterans have been neglected. In spite of his classic description of the pathologic condition in the blood vessels, Buerger² did not mention changes in nerves except to say that when the vascular lesions become chronic, arteries, veins and nerve trunks of the legs are often bound together in a mass of fibrous tissue. Brown, Allen and Mahorner³ mentioned briefly that fibrosis, demyelination and increase

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1 Goldsmith, G. A., and Brown, G. E. Pain in Thrombo-Angitis Obliterans. A Clinical Study of One Hundred Consecutive Cases, *Am J M Sc* **189** 819-833 (June) 1935

2 Buerger, L. The Circulatory Disturbances of the Extremities Including Gangrene, Vasomotor and Trophic Disorders, Philadelphia, W. B. Saunders Company, 1924

3 Brown, G. E., Allen, E. V., and Mahorner, H. R. Thrombo-Angitis Obliterans. Clinical, Physiologic and Pathologic Studies, Philadelphia, W. B. Saunders Company, 1928

in the number of nuclei of the sheath of Schwann may occur in peripheral nerves and that inflammatory changes occasionally are present in the vasa nervorum. Diez⁴ has stated that increase in the neurilemma and fibrosis of the perineurilemma of the peripheral nerve trunks are noted in thromboangitis obliterans. He observed proliferation of the nuclei of the sheath of Schwann and resorption of myelin only in digital nerves, and because the vasa vasorum of nerve trunks appeared normal, he concluded that there was no anatomic basis for ascribing any of the pain to ischemic neuritis.

This study is based on the histopathologic observations on the peripheral nerves in 20 cases of thromboangitis obliterans. This diagnosis was made in each case because of the presence of a clinical picture typical of the disease and because of the presence of typical histopathologic lesions of thromboangitis in the blood vessels of the amputated specimen.

MATERIAL

The material was obtained from an amputated leg in 17 cases. Longitudinal and cross sections were made of the upper and lower portions of the anterior and posterior tibial nerves. Six of the 17 amputations had been performed above the knee, and from these legs longitudinal and cross sections were made of the popliteal nerves also. Cross sections of superficial nerves of the feet and digital nerves of the toes were taken from 7 of the legs, and cross sections of digital nerves also were examined from 2 amputated toes and 1 amputated finger. The sections of the nerves were stained with hematoxylin and eosin, Van Gieson's stain, Weigert's stain for myelin sheaths and Orlandi's stain (modified silver impregnation).

For comparison, sections were taken from popliteal nerves, upper and lower anterior and posterior tibial nerves, superficial nerves of the feet and digital nerves of the toes from 6 legs amputated because of neoplasm of the bone. The blood vessels were examined in these cases and found to be essentially normal grossly and histologically. The nerves in these legs were assumed to be normal and were used as controls.

LESIONS OF THE POPLITEAL, ANTERIOR TIBIAL AND POSTERIOR TIBIAL NERVES

Definite histopathologic changes were observed in these nerves in all but 1 case (figs 1 to 5). They are listed under separate categories. In only a few instances was there much difference in the appearance of the anterior and that of the posterior tibial nerves at corresponding levels.

Fibrosis—Increase of perifascicular and intrafascicular fibrous tissue was the most consistent pathologic change noted, and it occurred in all but 5 of the cases. Usually, but not always, it was more marked

⁴ Diez, J. Thromboangitis obliterans anatomia patologica, Prensa medica Argentina **21** 949-969 (May 23) 1934.

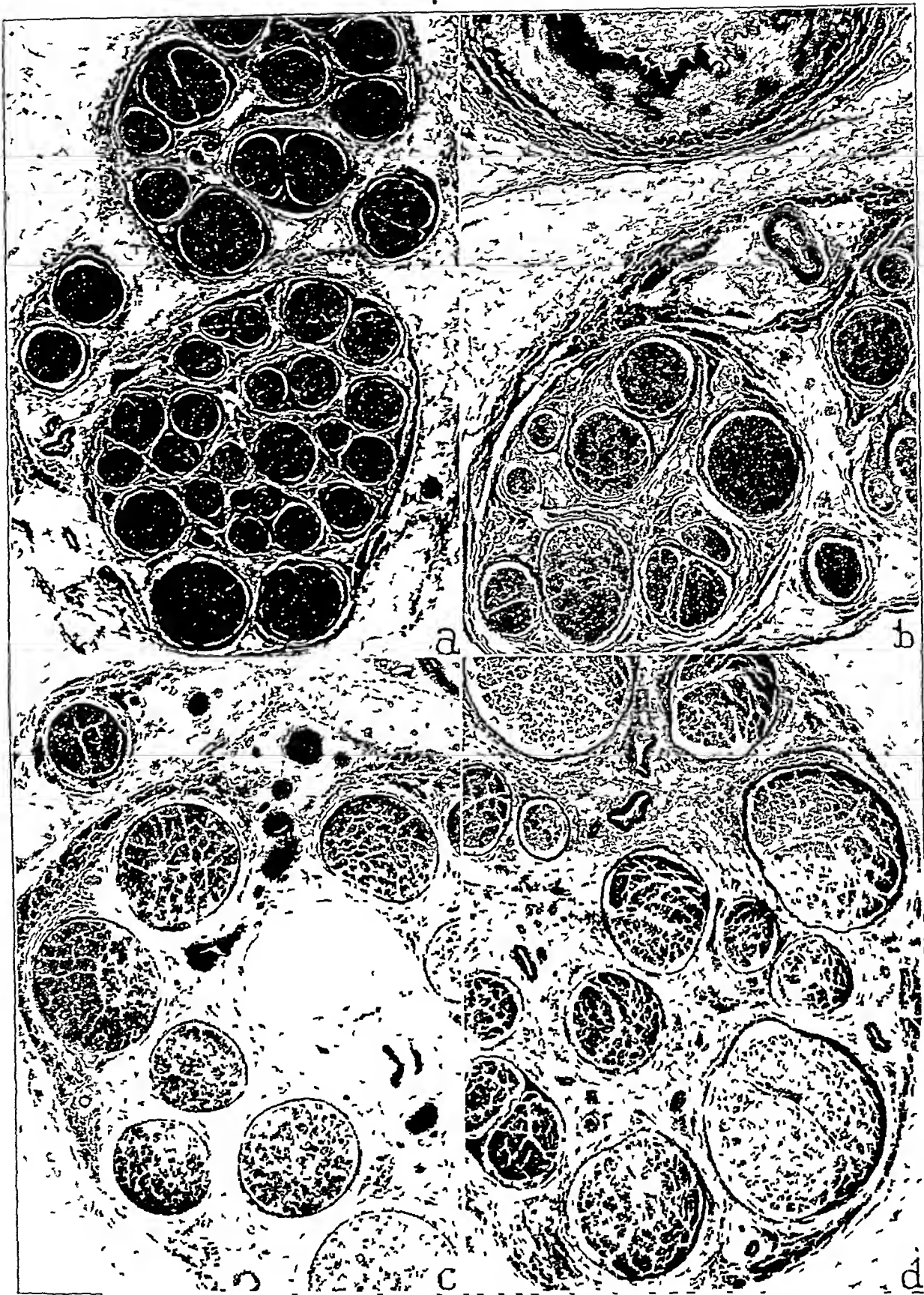


Fig 1—Cross sections of posterior tibial nerves, $\times 20$ Weigert's stain for myelin sheaths was used *a*, normal nerves *b*, thromboangitis obliterans, showing increased per fascicular fibrosis without definite perineural fibrosis The completely occluded artery is also shown, and the vasa nervorum have definitely thickened walls *c*, thromboangitis obliterans Perifascicular fibrosis and simple thrombosis of many of the vasa nervorum are shown *d*, thromboangitis obliterans Perifascicular fibrosis, edema of the fasciculi and atrophy of the fibers are shown

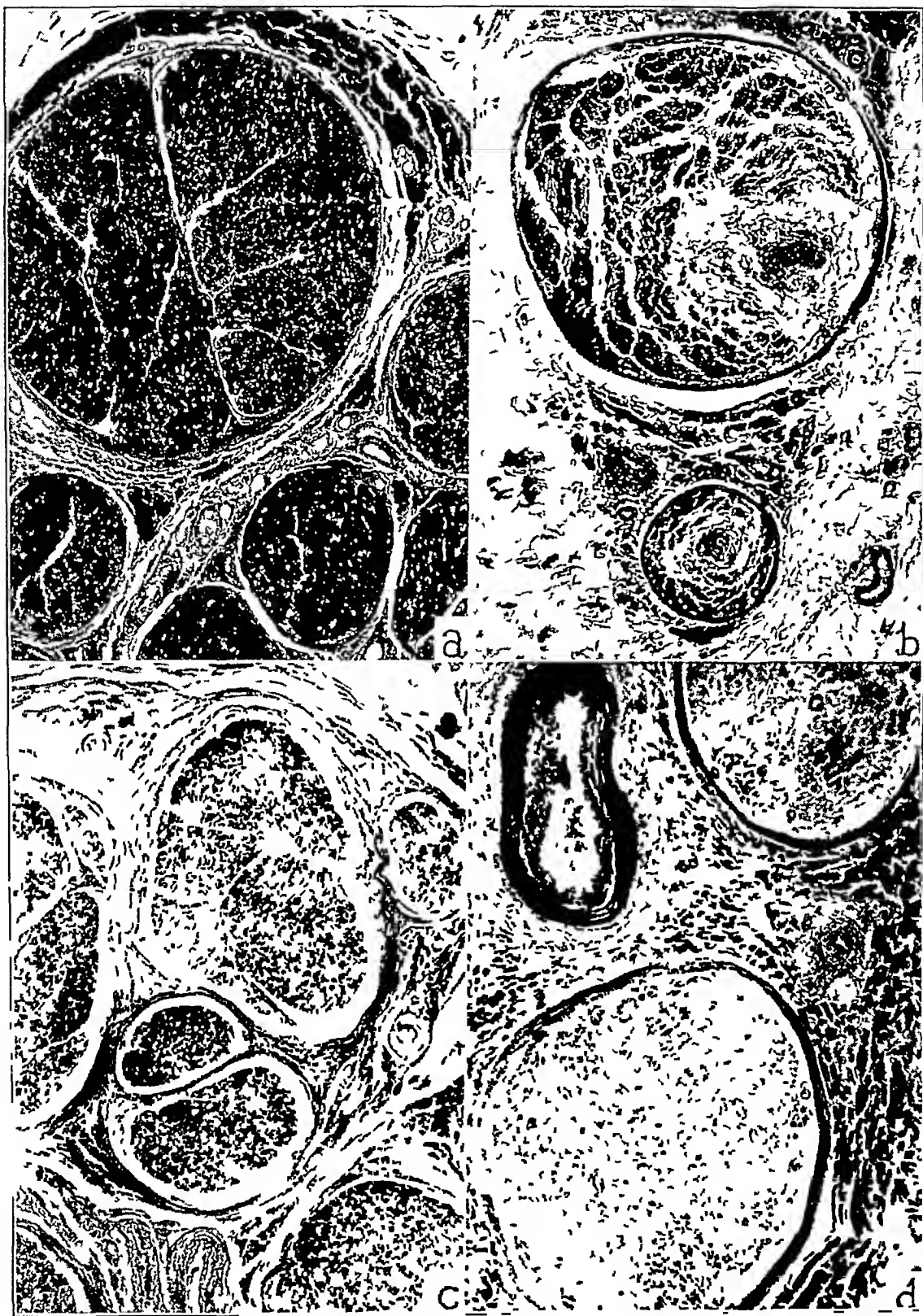


Fig 2—Cross sections of posterior tibial nerves, $\times 60$, Weigert's stain for myelin sheaths *a*, normal nerve Note the even, dark staining of myelin *b*, thromboangitis obliterans There is marked local destruction of nerve fibers inside the fasciculi, with intrafascicular edema *c*, thromboangitis obliterans Note the extensive fibrosis and localized demyelination *d*, thromboangitis obliterans There is almost complete demyelination of the fasciculi Note the inflammatory reaction in the arteriole

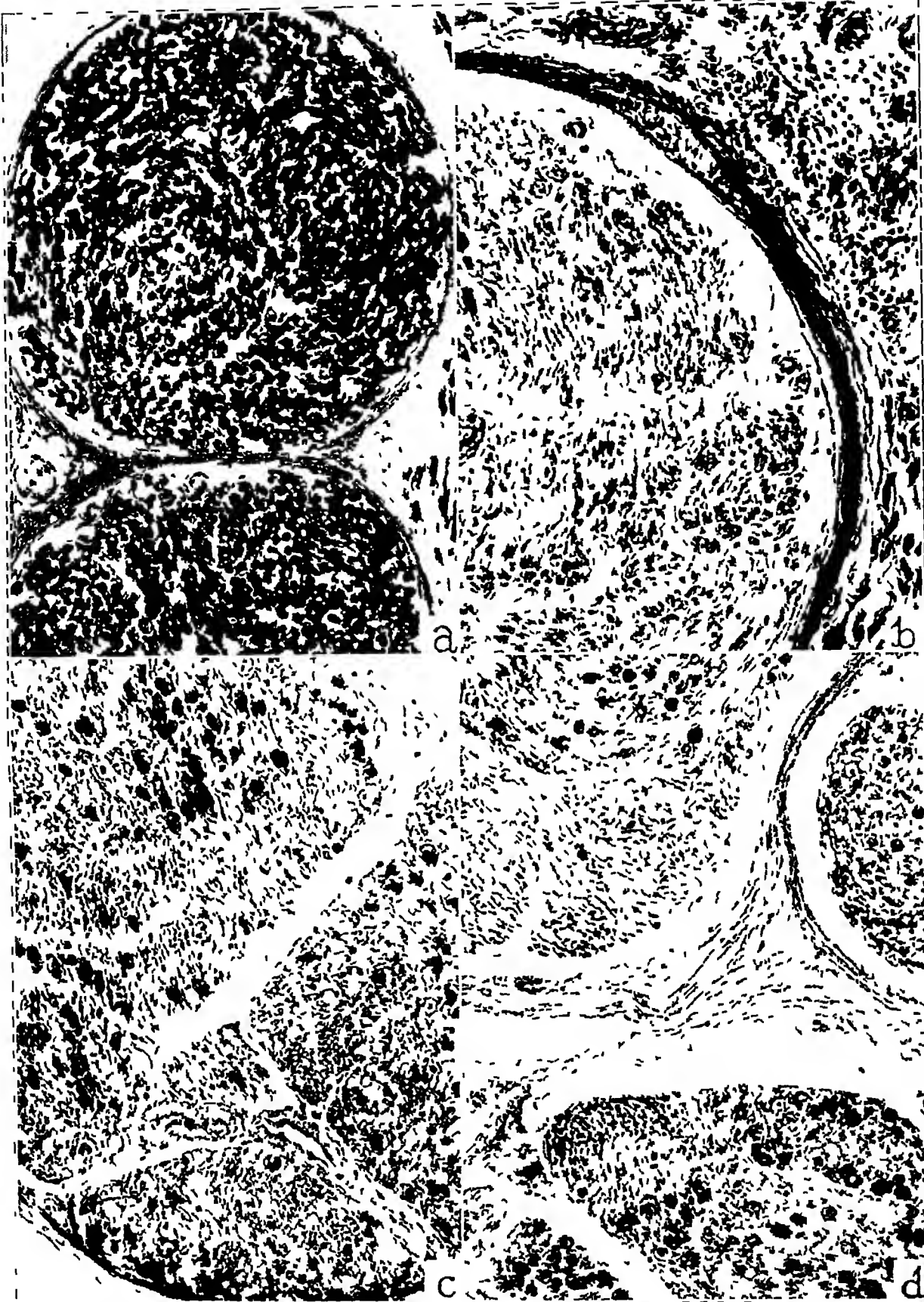


Fig 3—Cross sections of posterior tibial nerves, $\times 60$, Weigert's stain for myelin sheaths *a*, normal nerve Note the regular arrangement of nerve fibers with deeply stained myelin sheaths *b*, thromboangitis obliterans Note the edema, demyelination and destruction of nerve fibers and the numerous lymphocytes near the margin of the fasciculus in the upper left corner *c*, thromboangitis obliterans Only scattered myelin sheaths remain The vasa nervorum have definitely thick walls *d*, thromboangitis obliterans Note the perifascicular fibrosis and considerable demyelination

Fig 4—Longitudinal sections of posterior tibial nerves, $\times 160$, Weigert's stain for myelin sheaths *a*, normal nerve Note the regular arrangement of the deeply stained myelin sheaths *b*, thromboangitis obliterans Note the intrafascicular lymphocytes and marked angitis of the small artery *c*, thromboangitis obliterans Note the perifascicular and intrafascicular lymphocytes and the fragmentation of myelin *d*, thromboangitis obliterans Note the fragmentation of myelin *e*, thromboangitis obliterans Note the scattered lymphocytes and extensive demyelination *f*, thromboangitis obliterans Note the extensive demyelination and destruction of the architecture of the nerve

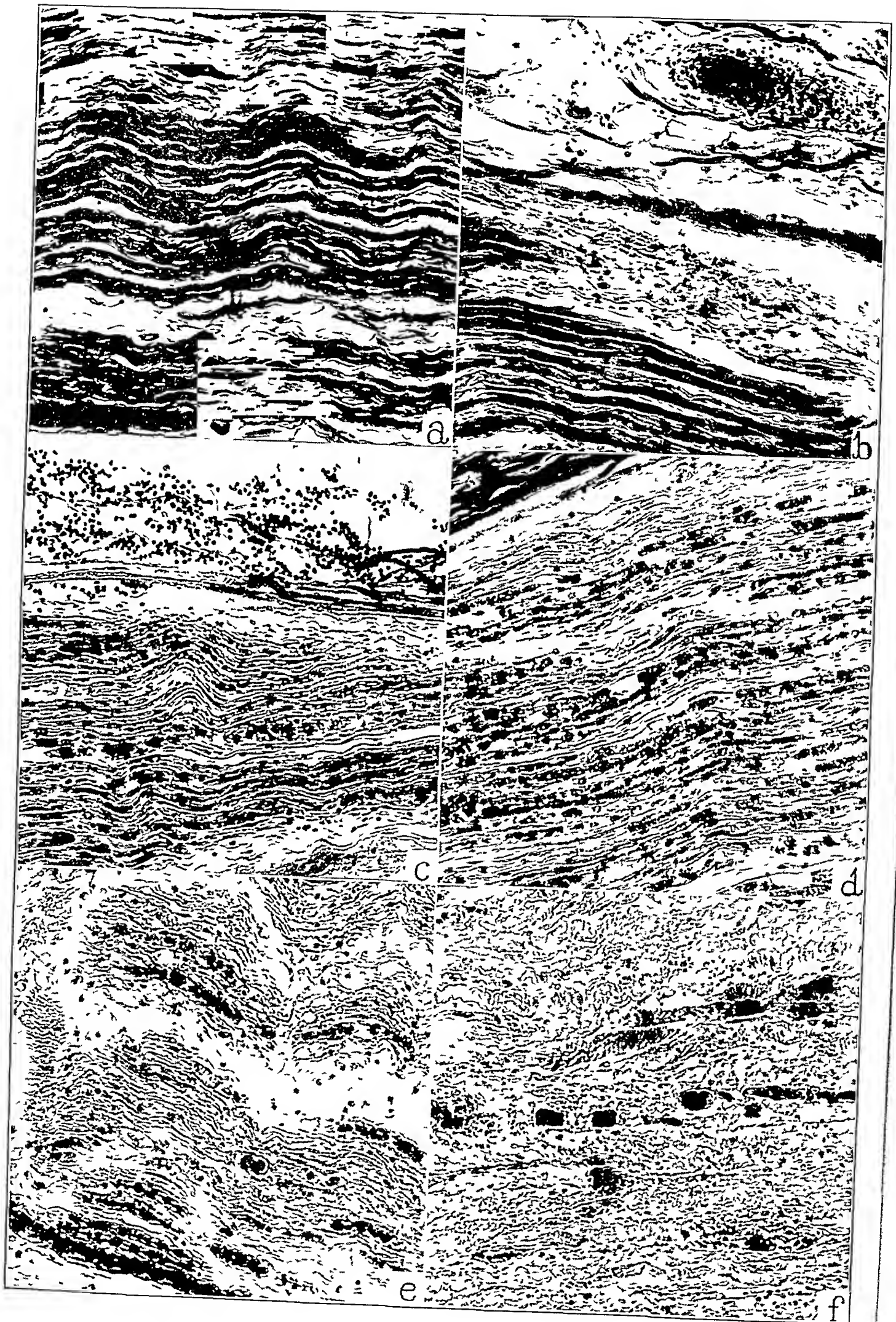


Figure 4

in distal than in proximal sections of the nerves. It is well known that fibrous tissue can exist with a meager blood supply and that it tends to be increased in all organs and tissue suffering from severe ischemia. Extensive perineural fibrosis, binding artery, vein and nerve into one dense sheath, as previously described, was not noted in any of the cases studied.

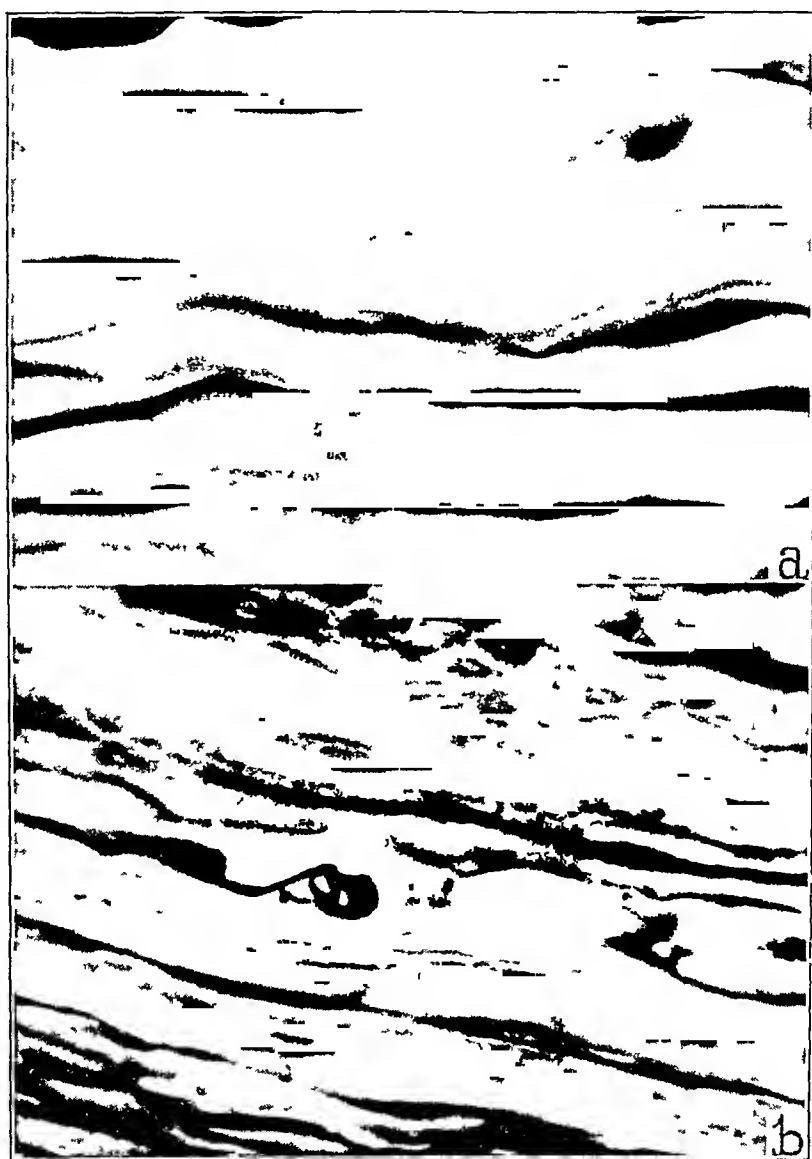


Fig 5—Longitudinal sections of posterior tibial nerves, $\times 865$, Orlandi's stain (modified silver impregnation) *a*, normal nerve, showing normal axis-cylinders *b*, thromboangitis obliterans. Note the broken axis-cylinder with a coiled end. Also note the spindle-shaped swelling of another axis-cylinder.

Wallenian Degeneration—It was noted that the myelin often stained irregularly in the control nerves, but complete demyelination of nerve fibers was not seen. In the nerves in 10 of the 17 cases of thrombo-

angitis obliterans, definite areas of demyelination, with intensification of the staining reaction of the remaining myelin, were noted. This condition was usually patchy, involving certain fasciculi in a given section and sparing others. Often only part of the fibers in a fasciculus were demyelinated. In longitudinal sections, variations were noted from patchy fragmentation of myelin to complete loss of myelin and destruction of the entire architecture of the nerve, with replacement by fibrous tissue. The use of Orlandi stains was somewhat disappointing, as axis-cylinders either appeared normal or could not be identified at all, possibly owing to artefacts or changes occurring between the time of amputation and that of fixation of the tissue. In a few of the diseased nerves, however, occasional fragmented and coiled-up axis-cylinders were seen, and there were abnormal swellings of other axis-cylinders. The extent of demyelination and destruction of the nerve fibers was always greater in the distal than in the proximal segments of the nerves, but in those cases in which it was noted it was present to some extent at all levels and in all the nerves studied.

Edema and Atrophy—Separation of the fasciculi, with thinning out of the fibrous tissue, was noted frequently. Some of this apparent change may have been due to an artefact, although it was not seen in the normal control nerves. Separation of nerve fibers themselves, with localized areas of marked atrophy and destruction, was noted in 4 of the cases in which there was extensive wallerian degeneration. This change is difficult to interpret but suggests rapid ischemic degeneration, almost infarction of the individual fasciculi.

Inflammation—Localized collections of lymphocytes and scattered lymphocytes, around and even within the fasciculi themselves, were noted in 9 cases. These areas were patchy, and they frequently involved only one of the main trunks. Their presence did not coincide with the presence of the other changes, in fact, they were usually observed in nerve segments where there was little or no wallerian degeneration. Their presence must be interpreted as part of an inflammatory reaction but whether this is one of the first evidences of ischemic degeneration of nerves or merely of an ascending infection along the nerve sheaths from a distal gangrenous region is not clear.

Changes in the Vasa Nervorum—Recent extensive thrombosis of the vasa nervorum was noted in 2 cases. In 6 cases small vessels, both arteries and veins, in the interfascicular and perineural regions showed the marked diffuse inflammatory reaction characteristic of thromboangitis. Perivascular lymphocytic collections were seen only twice in the vessels inside the fasciculi. In some instances the walls of these vessels were thickened, but in the majority of instances no changes were noted. It was not possible to explain the wallerian degeneration of the nerves on the basis of ischemia due to obstruction of the vasa vasorum.

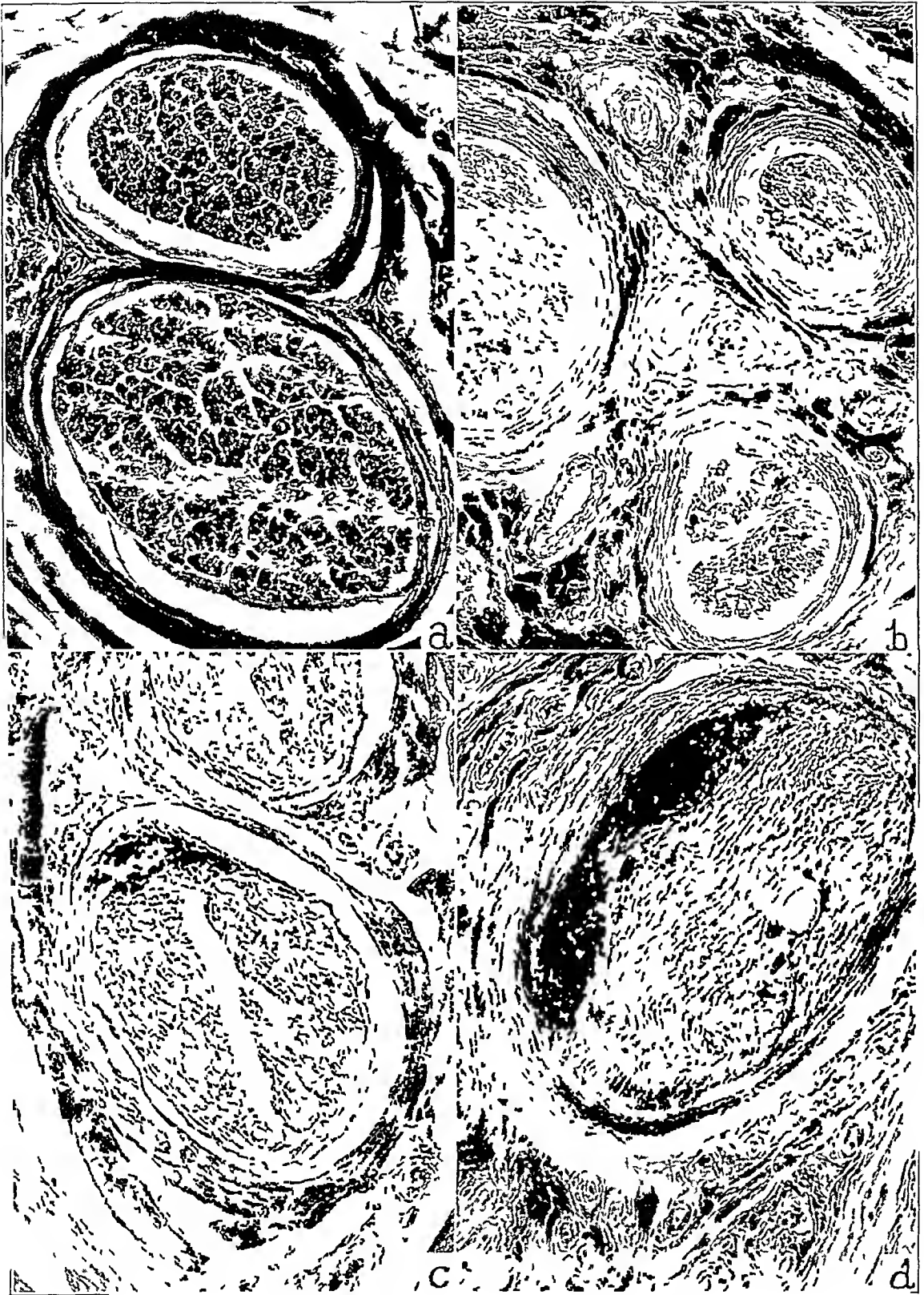


Fig 6—Cross sections of digital nerves, $\times 160$, Weigert's stain for myelin sheaths *a*, normal nerve *b*, thromboangitis obliterans Note the per fascicular fibrosis and partial demyelination *c*, thromboangitis obliterans There is complete demyelination Note the perineural fibrosis and small collection of lymphocytes inside the fasciculus *d*, thromboangitis obliterans There is complete demyelination Note the perineural fibrosis and large deeply stained mass of lymphocytes inside the fasciculus

Adequate justification for explaining all the nerve lesions on an ischemic basis exists in the extensive occlusion of the main arterial trunks which accompanied the nerves

LESIONS OF SUBCUTANEOUS NERVES OF THE FEET AND DIGITAL NERVES NEAR GANGRENOUS REGIONS

Sections of subcutaneous nerves of the feet and of digital nerves were examined in 10 cases (table 1 and fig 6). In 4 of these cases partial wallerian degeneration was seen in the proximal nerve trunks and it was complete in those nerves of the foot and toes that were examined. It was also present in 2 cases in which degeneration was not seen in the proximal nerve trunks. Definitely increased perineurial fibrosis was noted in all the nerves of the feet and toes. Also, it was interesting to note collections of lymphocytes inside the nerve bundles in 5 cases.

TABLE 1—*Clinical Findings Correlated with Changes in the Nerves of the Feet and Digits*

Case	Clinical Data		Histopathologic Lesions in Digital Nerves and Cutaneous Nerves of Feet*				
			Wallerian Degeneration in Proximal Nerve Trunks	Wallerian Degeneration in Local Nerves	Fibrosis	Edema	Inflammation
5	Neuritic	Leg and foot	2	4	3	0	0
6	Neuritic	Foot	3	4	3	0	1
7	Neuritic and local	Foot and fifth metatarsal	1+	4	3	2	0
8	Neuritic and local	Foot	2	4	2	1+	0
11	Local, margin of gangrene	Foot and base of toes	0	0	0	2	0
12	Local, margin of gangrene	Foot and fifth toe	0	3+	3	0	0
16	Local, margin of gangrene	Base of toe	0	2	0	3	2
18	Local, margin of gangrene	Second toe and meta tarsal region		2	1	1	2
19	Local, margin of ulcer	Second toe		0	4	0	2
20	Local, margin of ulcer	Second finger		0	2+	1+	2

* Graded on a basis of 1 to 4

CLINICAL ASPECTS

Goldsmith and Brown have described, under the term ischemic neuritis, a clinical manifestation which occurs in certain chronic progressive types of thromboangiitis obliterans. In those cases there is usually partial or complete occlusion of the femoral artery. Pain is the prominent feature and this pain occurs in large areas of the limb and is not necessarily limited to the sensory distribution of a certain nerve trunk. It is of variable intensity and occurrence but is usually severe and intractable. It is often associated with various types of paresthesia and sometimes with hypoesthesia, muscular weakness and diminution of

absence of deep reflexes. Episodes of severe vasospasm, characterized by mottled, deep cyanosis of the skin of the foot or of the entire lower portion of the leg may accompany the paroxysms of pain.

Similar pains involving the entire foot but not the leg are also occasionally described by patients. Local gangrene may be present in these cases, but the pain extends a considerable distance from the margin of the region of gangrene, tends to be paroxysmal and is usually accompanied by paresthesia.

TABLE 2—*Clinical Findings Correlated with Changes in the Anterior and Posterior Tibial Nerves*

Case	Type of Pain	Situation	Clinical Data						Histopathologic Lesions of Peripheral Nerves*					
			Duration, Months	Vasospasm	Paresthesia	Hypoesthesia	Muscular Weakness	Diminished Reflexes	Wallern Degeneration	Fibrosis	Edema	Lymphocytic Infiltration	Angitis of Vasa Nervorum	Simple Thrombosis of Vasa Nervorum
1	Neuritic	Leg and foot	6	Yes	Yes	Yes	Yes	Yes	3+	3	0	0	0	0
2	Neuritic	Leg and foot	2	Yes	Yes	Yes	Yes	Yes	2	2	1	0	0	0
3	Neuritic	Leg and foot	6	Yes	Yes	0	0	0	2	3	3	0	0	0
4	Neuritic	Leg and foot	7	Yes	Yes	0	0	0	2	2	3	0	1	1
5	Neuritic	Leg and foot	2	0	0	0	0	0	2	1	1	2	2	0
6	Neuritic	Foot	2	0	0	Yes	0	0	3	0	0	0	0	0
7	Neuritic and local	Foot	3	0	0	0	0	0	1+	1	2	1	0	0
8	Neuritic and local	Foot	2	0	0	0	0	0	2	0	3	0	0	0
9	Neuritic and local	Foot	2	0	0	0	0	0	1	2	3	2	2	0
10	Neuritic and local	Foot	1	0	Yes	0	0	0	2	2	1	1	0	0
11	Local, margin of gangrene	Foot and base of toes	4	0	0	0	0	0	0	1+	2	3	2	0
12	Local, margin of gangrene	Foot and base of toes	2	0	0	0	0	0	0	1	1	0	0	0
13	Local, margin of gangrene	Foot and base of toe	1	0	0	0	0	0	0	0	0	3	0	0
14	Local, margin of ulcer	Base of toe	12	0	0	0	0	0	0	0	0	0	0	0
15	Local, margin of ulcer	Base of toe	12	0	0	0	0	0	0	2	1+	1	0	0
16	Local, margin of ulcer	Base of toe	4	0	0	0	0	0	0	0	1	3	2	0
17	Local margin of gangrene	Base of toe	3	0	0	0	0	0	0	3	1	1	1	0

* Graded on basis of 1 to 4

All the cases of thromboangitis in which the nerves were studied histopathologically were also reviewed carefully from the standpoint of the type and situation of pain and the objective neurologic findings. In table 2 these data are correlated with the pathologic changes in the anterior and posterior tibial nerves.

The typical "neuritic" pain described by Goldsmith and Brown, which occurs in paroxysms and is felt in large areas of the lower portion of the leg and foot, was present in cases 1 to 5. In cases 1 to 4 there

were also extensive recurrent vasospasm and paresthesia. In cases 6 to 10 there were paroxysmal pains in the entire foot, involving regions at some distance from any local ulceration or gangrene. In the remaining cases (cases 11 to 17) the pain was localized to the region of ulceration or gangrene.

It is noteworthy that in all the cases in which the neuritic type of pain occurred, there was definite wallerian degeneration of the anterior and posterior tibial nerves and that this was not present in the cases in which there was only local pain in the regions of ulceration or gangrene. Definite correlation was not noted between the other pathologic findings—fibrosis, edema and lymphocytic infiltration, on the one hand, and the type and the situation of the pain, on the other hand. However, the lesions are definite, and they may represent stages in the process of degeneration of nerves. In cases of severe pain (cases 1 to 5) it was not possible to determine accurately the level of the nerve lesion responsible for the pain, but it is assumed that it was proximal to the level where degeneration was seen. Some wallerian degeneration was seen as far up as the level of amputation. In cases 1 to 5 the demyelination was increasingly more extensive in the more distal sections, therefore, it is assumed that levels of demyelination of individual fibers were scattered throughout various levels in the nerve trunks.

COMMENT

Wallerian degeneration of peripheral nerves is seen as an accompaniment of a number of lesions of nerves of different origin. It was noted by Woltman and Wilder⁵ in association with diabetes. Most of their patients had definite arteriosclerotic arterial occlusions also, and the authors concluded that the basis for the lesions of the nerves was ischemia. They did not find any definite correlation between the extent of the lesions of the nerves and the clinical manifestations, such as pain, paresthesia, hypoaesthesia and muscular weakness. Priestley⁶ found definite wallerian degeneration as the outstanding nerve lesion in association with arteriosclerosis obliterans of the legs in nondiabetic patients. Lesions of the nerves in thromboangitis obliterans noted in this study were considerably more extensive than those noted either by Woltman and Wilder or by Priestley, and there seemed to be a definite correlation between the presence of a neuritic type of pain and wallerian degeneration of the peripheral nerves.

5 Woltman, H. W., and Wilder, R. M. Diabetes Mellitus. Pathologic Changes in the Spinal Cord and Peripheral Nerves, *Arch. Int. Med.* **44**: 576-603 (Oct.) 1929.

6 Priestley, J. B. Histopathologic Characteristics of Peripheral Nerves in Amputated Extremities of Patients with Arteriosclerosis, *J. Nerv. & Ment. Dis.* **75**: 137-143 (Feb.) 1932.

One practical point concerns the question of surgical section of and injection of alcohol into peripheral nerve trunks, as advocated by Laskey and Silbert⁷ and by Smithwick and White,⁸ for the relief of intractable pain in thromboangitis. The operation is usually done in the lower third of the leg to avoid as many motor fibers as possible. Two of the series of patients with which this paper is concerned, who had neuritic pains of the feet, had undergone section of the posterior tibial, sural, superficial peroneal and deep peroneal nerves. The pain was not relieved. This can be explained by the fact that definite wallerian degeneration was observed proximal to the level of surgical section of the nerves in both cases. It does not seem logical to expect relief of the neuritic type of pain in thromboangitis obliterans by section of or by injection of alcohol into the peripheral nerves of the leg, as it is probable that ischemic inflammatory and degenerative lesions of nerves already have occurred at levels proximal to the site of the proposed section or injection.

The pain of ischemic neuritis is intractable to treatment, and when the lesions of the nerves are seen, this is not difficult to understand. Occasionally, after a period of weeks or months, it disappears spontaneously, possibly owing to ultimate cessation of degeneration. It is not known how completely regeneration may occur.

SUMMARY

In a histopathologic study of the peripheral nerves in a series of 20 cases of thromboangitis obliterans, various combinations of wallerian degeneration, fibrosis, edema, atrophy, lymphocytic infiltration, inflammation and thrombosis of the vasa vasorum were noted in all but 1 case. A definite correlation was found between the presence of wallerian degeneration and the clinical syndrome of ischemic neuritis.

7 Laskey, N. F., and Silbert, S. Thrombo-Angitis Obliterans. Relief of Pain by Peripheral Nerve Section, *Ann Surg* **98** 55-69 (July) 1933.

8 Smithwick, R. H., and White, J. C. Peripheral Nerve Block in Obliterative Vascular Disease of the Lower Extremity. Further Experience with Alcohol Injection or Crushing of the Sensory Nerves of the Lower Leg, *Surg, Gynec & Obst* **60** 1106-1114 (June) 1935.

BOECK'S SARCOID

REPORT OF A CASE, WITH CLINICAL DIAGNOSIS CONFIRMED
AT AUTOPSY

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The scarcity of autopsy material in connection with Boeck's sarcoid is explained by the fact that sarcoid runs a slow course, most often showing a preference for cutaneous manifestations. Nickerson,¹ in 1937, reported 6 cases in which autopsies were performed, describing for the first time lesions in the myocardium, endocardium, pancreas, testis and vertebral and femoral marrow, also differentiating the microscopic picture of sarcoid from that of tuberculosis.

Hunter² recently reported a case of sarcoid, with a review of the historical literature. His patient presented extensive changes in the lungs which completely cleared up under a strict hygienic regimen.

Longcope and Pierson,³ in reporting 8 cases, in 7 of which there were pulmonary changes, included a full bibliography. They stressed the importance of recognizing that although the disease is more often described as a disease of the skin, the generalized nature of the process is to be borne in mind.

Since the publication, in 1915, of the article by Kuznitzky and Bittorf⁴ demonstrating the pulmonary changes by means of roentgenograms for the first time, there have been numerous communications establishing the disease as a generalized condition. The disease may be recognized not only by the cutaneous lesions but also by manifestations elsewhere, such as pulmonary, osseous or ocular changes, which may give rise to the presenting symptoms.

From the New England Deaconess Hospital

1 Nickerson, D. A. Boeck's Sarcoid. Report of Six Cases in Which Autopsies Were Made, *Arch Path* **24** 19-29 (July) 1937.

2 Hunter, F. T. Hutchinson-Boeck's Disease (Generalized "Sarcoidosis"). Historical Note and Report of Case with Apparent Cure, *New England J Med* **214** 346-352, 1936.

3 Longcope, W. T., and Pierson, J. W. Boeck's Sarcoid (Sarcoidosis), *Bull Johns Hopkins Hosp* **60** 223-296, 1937.

4 Kuznitzky, E., and Bittorf, A. Boecksches Sarkoid mit Beteiligung innerer Organe, *Munchen med Wchnschr* **62** 1349-1353, 1915.

Doub and Menagh,⁵ in 1929, reported 2 cases in which the bones of the hands and feet showed cystic changes. Mylius and Schurmann,⁶ in 1929, reported 2 cases of sarcoid in which the patients were followed clinically and later came to autopsy. In case 1 the first manifestation was iritis. Later in the course of the disease the osseous and pulmonary changes were demonstrated by roentgen examination. At autopsy, tuberculosis, in addition to sarcoid, was evident. In case 2, autopsy was limited to the chest, revealing huge glands which showed only sarcoid. There were rare foci of caseation in the lungs. From their experience the authors said they felt that sarcoid is a special type of tuberculosis. Hantschmann,⁷ in 1930, reported 6 cases of sarcoid with pulmonary changes. Kirklin and Morton,⁸ in 1931, presented several cases in which osseous and pulmonary changes were well illustrated. Kissmeyer's⁹ monograph, published in 1932, gave a complete presentation with numerous illustrations.

REPORT OF CASE

History—Our patient was 1 of 6 children, 3 of whom were still alive and well, 1 had died of cardiac disease and 1 had died of Hodgkin's disease (sarcoid?). Our patient died at the age of 51. Prior to this illness he had been well except for "neuritis" at the age of 34 and appendicitis at the age of 43. He married at the age of 40, and there were no children.

The onset of the illness, in May 1934, was characterized by pain, swelling and stiffness in the hands and feet, and fever of three weeks' duration, the symptoms gradually becoming worse. He showed rather severe generalized periarticular involvement, which was partially ameliorated by the use of salicylates and aminopyrine. During this illness there were progressive anemia, loss of weight, weakness and cough.

Physical Examination—Examination revealed fusiform swelling of the fingers and wrists and edema of the ankles. The liver was palpable 3 fingerbreadths below the costal margin. There was generalized peripheral glandular enlargement, especially in the axillary and inguinal regions.

Laboratory Study—Extensive laboratory studies were made. The red blood cell count was 4,000,000, the hemoglobin value was 70 per cent, the white blood cell count was 20,000, the urine was normal, the Wassermann and Kahn tests

5 Doub, H. P., and Menagh, F. R. Bone Lesions in Sarcoid. A Roentgen and Clinical Study, *Am J Roentgenol* **21** 149-155, 1929.

6 Mylius, K., and Schurmann, P. Universelle sklerosierende tuberkulose grosszellige Hyperplasie, eine besondere Form atypischer Tuberkulose, *Beitr z Klin d Tuberk* **73** 166-209, 1929.

7 Hantschmann, L. Ueber torpide Formen disseminierter Tuberkulose, *Beitr z Klin d Tuberk* **73** 688-709, 1930.

8 Kirklin, B. R., and Morton, S. A. Roentgenologic Changes in Sarcoid and Related Lesions, *Radiology* **16** 328-333, 1931.

9 Kissmeyer, A. La maladie de Boeck. Sarcoides cutanees benignes multiples, Copenhagen, Levin & Munksgaard, 1932.

gave a negative reaction, the gonococcus complement fixation test gave a doubtful reaction, the sedimentation time was twenty to thirty minutes, the cultures of blood were sterile and chemical study of the blood gave normal values

Roentgen examination of the chest (fig 1) revealed dense symmetric bilateral glandular enlargement with fine lacelike infiltration extending out from roots of both lungs. The appearance of the chest was that of lymphoblastoma. Studies of the gastrointestinal tract revealed no unusual findings. Retrograde pyelography also showed a normal condition. Examination of the skeleton revealed hypertrophic changes about the bodies of the twelfth dorsal and the first and second lumbar vertebrae and both hips. Intravenous injection of dye showed a normal gallbladder. Roentgenograms of the hands and wrists were normal. There was narrowing



Fig 1—Roentgenogram of the chest taken at the onset of the illness, showing the huge bilateral symmetrically enlarged hilar nodes, with cordlike infiltration extending out into the parenchyma of the lung

of the joint space of the right knee. The sinuses were normal. In view of the changes in the lungs suggesting lymphoblastoma, roentgen therapy was given over this area. Since the glands did not disappear, it was thought that the changes were not those of lymphoblastoma. In view of the infectious arthritis, typhoid vaccine was given, with some improvement.

Course—The patient was discharged improved from the hospital. The diagnosis was infectious polyarthrititis, hypertrophic osteoarthritis and bilateral adenitis of the roots of the lungs.

Shortly after discharge he came under our observation, and in addition to the aforementioned data, it was learned that the gonococcus complement fixation test gave a positive reaction. The patient repeatedly denied the possibility of

infection. Subsequent tests gave positive results. He had been free from cough for one week, and the anemia had subsided. The striking features of the physical examination were edema of the ankles and fusiform swelling of the phalangeal joints. At the time there was no enlargement of the peripheral nodes. With a high protein diet the edema subsided and the joints became flexible, and in October 1934 it was thought he would soon regain his health.

On October 23 the patient had renal colic due to a small calculus. In November there was return of the articular symptoms, with subsidence in January. At this time there were symptoms of a duodenal ulcer, and the diagnosis was confirmed roentgenographically. Despite hospitalization and dietary treatment, the ulcer failed to respond to medical management, and in May 1935 posterior gastroenterostomy was necessary. This operation was completely successful, and there



Fig 2—Roentgenogram of the chest taken ten months later than the one shown in figure 1. The appearance is essentially normal.

were no further symptoms referable to the duodenal ulcer. During this time the patient was free from symptoms referable to the joints. A roentgenogram of the chest was entirely normal, no enlargement of the hilar nodes being visible (fig 2).

Four weeks after operation (June 1935) there was a recurrence of the arthritic symptoms. He was again given a high protein diet. He was not seen for four months, after which he reported that the arthritis had lessened while he was living at the seashore in July but was worse in August. He showed recurrence of the fusiform swelling of the phalangeal joints, with marked limitation and similar involvement of the right elbow. He went to Florida for the winter, remaining until June 1936. He complained of swelling of both forearms and of inability to close his hands. He could walk only with pain. Laboratory studies at this time revealed no anemia. The calcium content of the

serum was 101 mg per hundred cubic centimeters. The protein content of the plasma was 66 mg per hundred cubic centimeters. The gonococcus complement fixation test gave a positive reaction. The tuberculin test gave a negative reaction. It was thought that the edema might be due to nutritional factors, despite the normal plasma protein value. He was given a high protein diet, without improvement.

In July there was definite secondary anemia, and the articular symptoms had increased. Shortly after this he had a severe cough and fever and was confined to bed.

Roentgen examination of the chest (fig 3) revealed the same picture as in 1934, and a diagnosis of sarcoid was made. On roentgen examination the hands



Fig 3—Roentgenogram of the chest taken two years and two months after the onset of the illness. The picture is essentially similar to that in figure 1. The discrete nodes are readily visible.

and feet appeared normal. At this time he showed over the forearms faint dry, scaly erythematous patches which were not characteristic of sarcoid and which suggested a tentative diagnosis of xeroderma. The edema was less. The cough was his chief symptom.

The patient's condition changed little until one week before death, when edema of the larynx developed, with a change in voice. On Oct 22, 1936, two and a half years after the onset of his symptoms, the patient collapsed, with air hunger and profuse sweating, and died in thirty minutes.

Gross Postmortem Examination—Autopsy was performed ten hours post mortem.

General The body was that of a slightly undernourished but normally developed man, about 140 pounds (63.5 Kg) in weight and 5 feet and 8 inches (173 cm) in height. The skin over the arms, chest and back showed light brown pigmentation and scaling, somewhat more prominent over the chest anteriorly. The scrotum was edematous. The extremities were normally developed but showed some irregular swelling of the knee and ankle joints. The greater portion of swelling appeared to be edema of soft tissues, most pronounced about the ankles and feet. The phalangeal joints of the hands were irregularly prominent. Exploration of the right knee disclosed smooth articular surfaces and normal-appearing synovial fluid.

Lungs The right pleural cavity contained 750 cc and the left 500 cc of serous slightly yellow fluid. The lungs were relatively voluminous. There were no adhesions. The lungs weighed 800 Gm each. The pleurae were smooth and grayish blue and not infrequently finely granular, owing to a minute grayish white hyaline deposition. In addition, over both apexes, especially posteriorly, there were large plaques, the largest being 3 cm long and 8 mm thick, of slightly elevated grayish white hyaline. This was not associated with scarring of the underlying lung. Two subpleural calcified nodules, about 5 mm in diameter, were at the posterior aspect of the lower lobe of the left lung 3 cm from the diaphragmatic margin. Similar nodules occurred posteriorly in the lower lobe and in the middle lobe of the right lung, but these calcified nodules on section showed also anthracosis. On section all the lobes were moderately subcrepitant, relatively firm and pinkish gray, with small poorly defined firmer foci of gray. A moderate amount of slightly blood-tinged fluid could be expressed from the cut surface. Occasionally throughout the lung, nodules, 3 mm or less in diameter, were encountered which were firm and black. The bronchi were filled with yellowish brown mucus, and the mucosa was swollen. The trachea and larynx, including the epiglottis, exhibited edema. The pulmonary arteries and veins were normal.

Heart The pericardial cavity contained 75 cc of clear slightly yellow serous fluid. The pericardium was thin, smooth and glistening throughout. The heart weighed 375 Gm and was normal except for moderate coronary sclerosis.

Spleen The spleen weighed 175 Gm. The capsule was slightly wrinkled, smooth and gray. The cut surface was moderately soft and grayish red. The trabeculae were indistinct. The follicles were small and generally poorly defined.

Gastrointestinal Tract The gastrointestinal tract was normal except for the old posterior gastrojejunostomy, with jejunal ulcer.

Liver The liver weighed 1,500 Gm. The capsule was thin, smooth and reddish brown. The cut surface was flat, normally lobulated and reddish brown. The central zones were indistinct.

Lymph Nodes The bronchopulmonary lymph nodes were enlarged bilaterally and symmetrically, the largest being 2.5 cm in diameter. They were discrete and soft and on section presented a bulging moist pink-gray surface which was homogeneous except for an occasional small focus of soft gray tissue. Inferior to the bifurcation of the trachea the lymph nodes were similarly enlarged, the largest being 3.5 cm in length. The nodes superior to the bifurcation and the peritracheal nodes presented a similar appearance and were up to 1.5 cm in length (fig 4). No nodes were palpated in the neck or axillae. Abdominal periaortic and iliac lymph nodes were similarly enlarged, the largest being 2 cm in greatest diameter. One node in the celiac region showed a focus of gray fibrous tissue 7 mm in diameter. The inguinal nodes were slightly enlarged and appeared similar to those elsewhere. The portal, gastric and mesenteric lymph

nodes showed no enlargement Bacteriologic examination of a bronchopulmonary node revealed no tubercle bacilli, and guinea pig inoculation gave negative results

Bones The lumbar vertebrae and ribs showed no abnormality The marrow of the lumbar vertebrae was normal

Microscopic Postmortem Examination—The microscopic examination showed the following

Heart Section of the left ventricle showed muscle fibers of average width or slightly attenuated, with no enlargement of the nuclei Throughout the myo-



Fig 4—A retouched photograph of the gross specimen The posterior aspect of the lungs shows the enlarged nodes, below the bifurcation, measuring 4.5 cm in greatest diameter

cardium were numerous, usually small and frequently perivascular areas of connective tissue which often appeared edematous and mildly infiltrated with lymphocytes and a few eosinophils There was slight extension of epicardial fat into the myocardium Occasionally within the connective tissue were small foci of irregularly oriented epithelioid-like cells, without giant cells and caseation but

with necrosis of collagen and a few lymphocytes. In the plane of this section the foci were not related to the blood vessels. The capillaries adjacent to the foci showed slight reduplication of the endothelium. The epicardium was thickened, and throughout the epicardial fat was a scattering of lymphocytes, with a few leukocytes, chiefly eosinophilic, which were more numerous near a large coronary artery. There was considerable intimal and medial thickening of the two large coronary arteries, accompanied by hyalinization and lipoid deposition. Arteries within the myocardium were generally not appreciably thickened.

Lung. Sections from the upper and lower lobes of the lungs exhibited similar histologic pictures. Scattered throughout, frequently in groups and somewhat more numerous in the vicinity of the small blood vessels and the bronchi, were numerous miliary lesions, which tended to remain in the alveolar wall. The lesions were typified by small collections of epithelioid cells which centrally were irregularly arranged and peripherally showed a disposition to concentric arrangement. Infrequently there were giant cells with three to fifteen nuclei simulating foreign body giant cells. Occasionally cells within the lesions were pigmented. There was no caseation, and the lesions tended to remain discrete, frequently being surrounded by collagenous connective tissue. Scattered throughout the connective tissue were a variable but generally small number of small mononuclear cells, chiefly lymphocytes. Intervening lung showed empty alveoli except for a scattering of desquamated cells and a few red blood cells. In some foci the alveoli were partly collapsed, and a few were hyperdilated. Some portions of the pleura showed no involvement or only an occasional lesion immediately beneath the pleura. The pleura of the upper lobe of the right lung was greatly thickened by fibrous and hyalinized connective tissue, throughout which were collections of small mononuclear cells, chiefly lymphocytes, only one group of cells that were suggestive but not typical of nodules was seen elsewhere. The section of the upper lobe of the left lung included a small pulmonary artery in which was hemispherical elevation of the intima, comprised of mononuclear cells, some of which were similar to those of the lesions previously described but in atypical arrangement. There were also a few lymphocytes. The remaining arteries and veins appeared normal.

The bronchi were normal although there were many peribronchial lesions. A section of the lower lobe of the left lung showed healed lesions resembling a primary tubercle, with central caseation and calcification and a peripheral zone of dense hyalinized connective tissue. There was considerable fibrosis of the adjacent lung. Another section of the lower lobe of the left lung showed similar scarring and a portion of a calcified focus surrounded by dense connective tissue. A section of the lower lobe of the right lung showed a subpleural nodule surrounded by dense hyalinized connective tissue and centrally comprised of acidophilic shadowy structural outlines, scattered throughout which was a small amount of black pigment. There was mild fibrosis in the immediate vicinity, with mild lymphocytic infiltration and occasional lesions not typical of tubercles but similar to and less poorly defined than the lesions previously noted.

The trachea showed numerous lesions both immediately beneath the mucosa and among the mucous glands, where there were considerable distortion, fibrosis, round cell infiltration and degeneration. The lesions here exhibited less tendency to peripheral concentric arrangement of cells, and the cells were more frequently irregularly than radially arranged. The underlying stroma was edematous, and the vessels were slightly hyperemic.

Spleen. The capsule was normal. Scattered throughout the spleen were numerous lesions comprised of epithelioid cells without caseation. The cells

were irregularly disposed, and there was no constant disposition to concentric peripheral arrangement. The periphery was generally surrounded by a few lymphocytes and was poorly defined from the adjacent pulp. Generally the stroma and the red pulp were moderately dense. The sinuses for the most part were empty, although occasionally they contained red blood cells. The malpighian

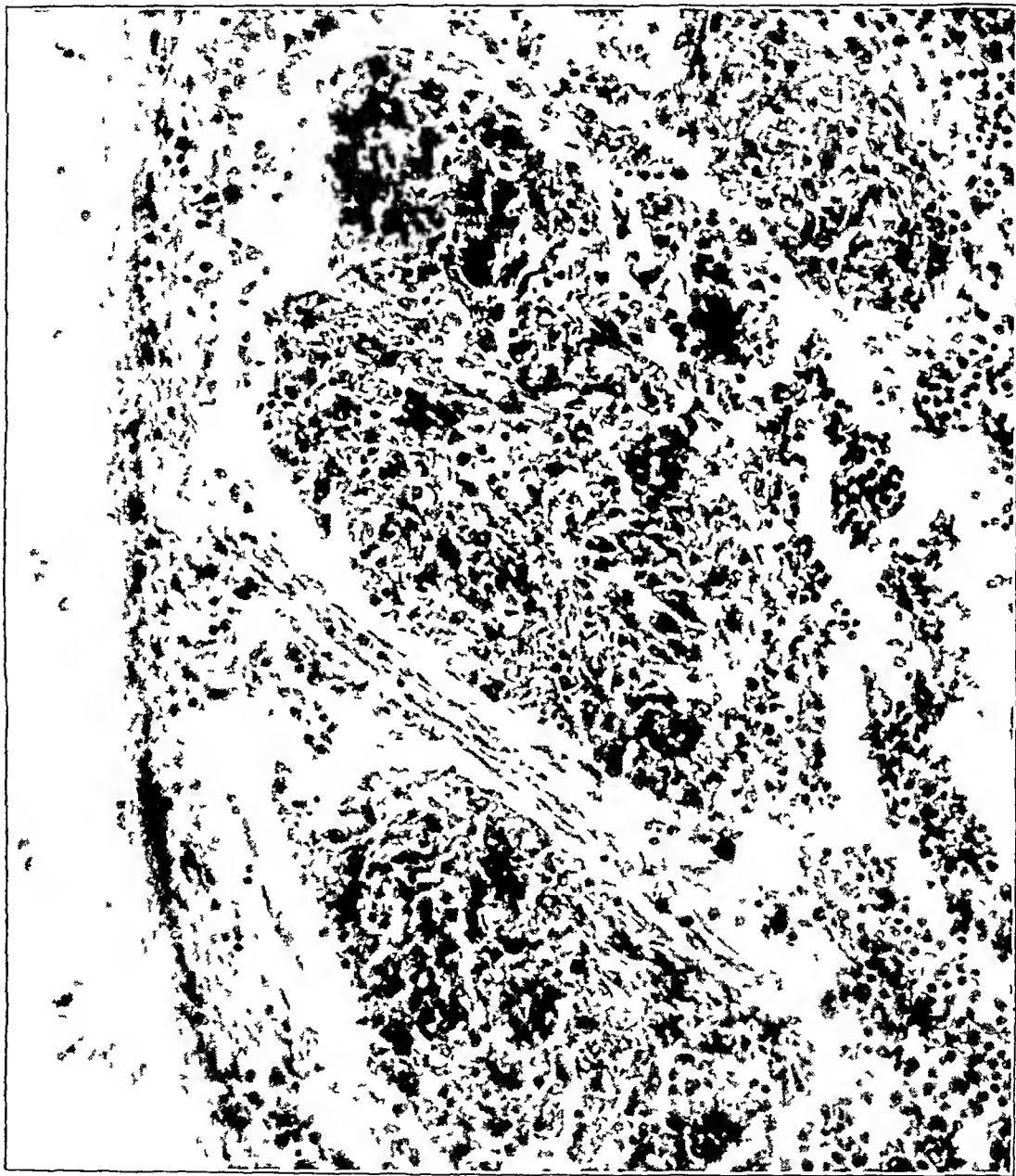


Fig 5—Photomicrograph of a section of the margin of a hilar node, showing sarcoid nodules and edema, $\times 300$

bodies exhibited slight activity and were moderately numerous. The trabeculae were small and appeared normal.

Liver There was frequently an increase of connective tissue in the portal zones. Scattered irregularly throughout the liver and confined to no particular zone were numerous lesions similar to those just described. Some showed con-

centric and others irregularly radial disposition of the peripheral cells, and there was frequently mild lymphocytic but rarely leukocytic infiltration at the periphery. Giant cells similar to those previously described were occasionally encountered within the lesion. Frequently there was a small amount of concentric collagen in the peripheral portion.



Fig 6—Photomicrograph of a section through the center of a hilar node, showing edema and dilated sinuses, $\times 48$

Kidney Three sections from the kidneys showed a similar picture. Infrequently within the cortex and medulla were lesions similar to those already described.

Lymph Node Sections of portal, abdominal, periaortic, peritracheal and bronchopulmonary lymph nodes and lymph nodes inferior to the bifurcation of the

trachea included areas of essentially similar change. There were numerous lesions similar to those described in the lungs although showing more variation. The lesions varied from small usually rather distinct collections of epithelioid-like cells, centrally irregularly arranged and peripherally either concentrically or irregularly radially disposed, to larger poorly defined lesions, with a few identifiable cells distributed throughout an acidophilic hyaline matrix that was usually rich in collagen (fig 5). Usually there was some peripheral collagen, and not infrequently there was some acidophilic intercellular hyalin centrally. There were giant cells of foreign body type occasionally within the lesions. No caseation but necrosis of collagen was noted. Where the lesions were numerous and widespread, much of the architecture of the node was obliterated by fibrosis. This was a prominent feature of the bronchopulmonary nodes. Otherwise the nodes exhibited marked edema and slight hyperplasia (fig 6). The sinuses within the nodes and the external lymphatic vessels were widely dilated and frequently contained fibrin. Section of a left inguinal node showed marked edema and dilatation of the sinuses but no definite lesions.

Skin Section of the skin from the chest showed a few small round cells about slightly ectatic vessels in the superficial corium. Immediately beneath the corium in the fat and not apparently in relation to the vessels were a few lesions similar to those just described. The basal cell layer of skin contained an increased amount of pigment. A scattering of cells in the papillary layer contained golden brown rather refractile pigment. The arteries were normal.

Aorta The intima and the inner portion of the media exhibited slight degeneration.

Thyroid Gland Several small lesions similar to those just described were irregularly scattered throughout the gland, otherwise it was normal. The parathyroid glands were normal.

Bone Sections of a lumbar vertebra and a rib showed slightly hyperplastic marrow.

Final Diagnosis—The final diagnosis was sarcoid, with involvement of the bronchopulmonary, tracheal, paravertebral, iliac and inguinal lymph nodes, lungs, trachea, heart, spleen, liver, thyroid gland, kidneys and skin, edema of the larynx and trachea, bilateral hydrothorax, a healed primary tuberculous complex (calcified), and duodenal and jejunal ulcers (with old posterior gastroenterostomy).

COMMENT

In this case, greatly enlarged bilateral hilar lymph nodes were at first presented, these cleared up completely and later recurred. Moreover, the autopsy revealed the mechanism involved, an intense and extensive edema of the nodes, with the presence of sarcoid lesions (fig 6). The roentgenograms and the photographs of the gross specimen (figs 1 to 4) plainly showed the large size and discrete character of the nodes, one measuring 4.5 cm in diameter, largely because of edema.

There was no evidence of active tuberculosis, in spite of vigorous search and animal inoculation. A tuberculin test two years before death gave a negative reaction. A healed primary pulmonary lesion, probably tuberculous, was present.

For the first time lesions in the kidney and thyroid gland are reported

Extensive and characteristic changes in the lungs, with surprisingly few symptoms, are usually present. The persistent cough in this case, an unusual feature, was probably due to the tracheal lesions, which were demonstrated at autopsy. The striking changes in the lungs, thought at first to be due to Hodgkin's disease, gave an immediate response to irradiation that was discouraging, yet in less than one year the roentgenographic appearance of the chest was absolutely normal (fig 2). After another year the patient became definitely worse, with progressive arthritis. At this time there was a recurrence of the pulmonary changes, and the true nature of the condition was determined.

SUMMARY

A case of Boeck's sarcoid is presented in which the patient was followed for two years, the diagnosis was made ante mortem and autopsy confirmed it. Lesions were present in the lung, skin, liver, spleen, myocardium, lymph nodes, trachea, thyroid gland and kidney. Edema of the lymph nodes may be an important factor in their enlargement. This case clarifies the mechanism involved in huge though variable lymph nodes.

It is again emphasized that sarcoid may be generalized and may present changes sufficient to make a tentative diagnosis possible not only on the basis of the cutaneous manifestation but also from changes in the lungs as well as in the bones.

ORAL RAGWEED POLLEN THERAPY

CLINICAL RESULTS OF EXPERIMENTS ON GASTROINTESTINAL ABSORPTION

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The evident disadvantages of hypodermic administration—discomfort, expense and liability to reactions—have resulted in repeated attempts to substitute oral administration in immunotherapy. Much has been said concerning the oral use of typhoid vaccine, cold vaccines and extracts of poison ivy. Although there is no evidence of great effectiveness of this method in the prevention of typhoid, the common cold and rhus dermatitis, the simplicity of the procedure has aroused interest among members of the medical profession and the public. It is but natural, therefore, that for a disease as common as hay fever such treatment should be suggested and tried.

In 1922 Touart¹ reported the results of treatment of 6 patients with hay fever by daily ingestion of a tablet containing 0.1 mg of pollen protein coated with phenyl salicylate. The patient with allergy to grass pollen obtained relief, but only 1 of those with allergy to ragweed pollen was relieved. Black,² experimenting on himself, found that ragweed antigen could be demonstrated in the blood and urine after the ingestion of fairly large amounts of pollen extract. The method he used to demonstrate ragweed antigen in the serum was to test himself intradermally with his own serum and also to test with the same serum the skin of a passively sensitized nonallergic person. Later, Black³ employed oral therapy for several patients with grass or ragweed sensitivity and compared the results with those for patients treated by the hypodermic method. Complete failures occurred in 20 per cent of the cases with oral therapy as against 6 per cent with the injection method.

From the Department of Medicine, Northwestern University Medical School

1 Touart, M D. Hay Fever. Desensitization by Ingestion of Pollen Proteins, New York M J **116** 199 (Aug. 16) 1922

2 Black, J H. The Oral Administration of Pollen, J Lab & Clin Med **12** 1156 (Sept.) 1927

3 Black, J H. The Oral Administration of Pollen. A Clinical Report, J Lab & Clin Med **13** 709 (May) 1928

In 22 2 per cent of the cases of pollen asthma, complete failure resulted with oral therapy, while with the hypodermic method no absolute failures were noted

In his treatise on hay fever Thommen⁴ cited a satisfactory result in a case of hay fever in which pollen was given orally. Such attempts in other cases gave variable results. Thommen was not favorably impressed with this method because of the large amounts of extract required and the variability of enteral absorption. Urbach⁵ has published a number of communications in which he has claimed to have obtained satisfactory results in hay fever by the use of peptones of the specific pollen administered orally. He has also reported similar results with the use of peptones made from the entire pollinating flower.

In 1933 and 1934 Gatterdam⁶ reported on the use of oral pollen therapy. In 75 to 85 per cent of a series of 85 patients thus treated marked relief was obtained. The pollen was given twice daily, with additional doses during attacks. The usual amount was from 3 to 15 drops of a 3 per cent extract. Occasionally mild urticaria or hay fever resulted from overdosage. The pollens used were those of cottonwood, ash, Bermuda grass, rabbit bush and false ragweeds.

The fact that a number of hay fever sufferers had claimed that they obtained relief by eating honey produced in their vicinity led McGrew⁷ to suspect that the pollen in the honey was responsible for the result. He therefore tried oral pollen therapy. A 1 per cent extract of pollen was employed coseasonally, 1 to 10 drops being given three times daily or for the immediate relief of an individual attack. Overdosage caused aggravations of symptoms. Of 33 patients thus treated, 29 were improved. Those with multiple allergy or with asthma did not do so well.

The most favorable report was that of Stier and Hollister,⁸ who obtained satisfactory results in 78 per cent of a large series of cases in an experience extending over three years. Their best results were

4 Thommen, A. A. *Asthma and Hay Fever in Theory and Practice*, Springfield, Ill., Charles C. Thomas, Publisher, 1931, p. 764.

5 Urbach, E. Desensibilisierung pollenallergischer Individuen auf oralem Wege mittels artspezifischer Pollenpeptone, *Klin. Wchnschr.* **10** 534 (March 21) 1931, Die Behandlung des Heufiebers mittels artspezifischer Gräserblüten-Propeptane bzw. Pollen-Mikromahlzeiten, *ibid.* **12** 1797 (Nov. 18) 1933, Pathogenese und Therapie des Heufiebers, *Wien klin. Wchnschr.* **47** 1073 (Aug. 31) 1934, Die biologische Behandlung des Heufiebers, *München med. Wchnschr.* **84** 488 (March 26) 1937.

6 Gatterdam, E. A. Oral Administration of Pollen Extracts, *Southwestern Med.* **17** 199 (June) 1933, Hay Fever in Central Arizona and Its Treatment with Oral Extracts, *ibid.* **18** 130 (April) 1934.

7 McGrew, G. D. Time and Money Saved in the Treatment of Hay Fever, *Mil. Surgeon* **80** 371 (May) 1937.

8 Stier, R. F. E., and Hollister, G. Desensitization by Oral Administration of Pollen Extracts, *Northwest Med.* **36** 166 (May) 1937.

obtained with the coseasonal method of administration. The pollens used consisted of a large variety but did not include ragweed pollen. The doses consisted of 3 drops of a 1:100,000 dilution of pollen to a maximum dose of 21 drops of a 1:100 dilution. Most patients required a quantity of the 1:100 solution daily. In a few instances mild systemic symptoms were observed.

Bernstein and Kirsner,⁹ administering a 5 grain (0.3 Gm.) capsule of ragweed pollen orally, were unable to demonstrate enteral absorption sufficient to cause a reaction in the passively sensitized skin of 4 non-allergic persons. No mention was made of any attempt to compare by the same technic the presence of the ragweed antigen in the circulation after it had been administered hypodermically. These authors also corroborated previously recorded observations that digestion of pollen by gastric juice caused only a moderate diminution of the cutaneous reactivity of ragweed pollen.

Because almost all the successful results concern districts either entirely free from ragweed pollen or having comparatively little of it and because as a rule protection to pollen allergy other than that of ragweed is more easily attained, it was thought best to make a study of oral therapy of patients with ragweed sensitivity in a community representative of the Middle West.

EXPERIMENTS ON GASTROINTESTINAL ABSORPTION OF POLLEN

It was deemed advisable by us to make studies on gastrointestinal absorption of pollen before we ventured into the problem of oral therapy. This we considered essential in order to have at least a rough estimate of the doses to be used clinically.

We employed for this purpose a method previously used by us¹⁰ in demonstrating quantitatively the absorption rate and tide of injected antigens. In the experiments reported earlier we sensitized a number of sites on several persons with serial dilutions of serum containing ragweed reagin. Within a few minutes after the injection of a ragweed extract, reactions began to appear in the sensitized areas. The appearance time of the first reaction, the time at which the last reaction took place and the highest dilution of reagin at the site of which a reaction was obtained gave an indication of the rate and degree of absorption of the pollen antigen. With the average serum and the average subject, 0.5 mg. of pollen injected hypodermically was sufficient to cause a reaction.

For the purpose of the present experiment, one arm of each of 17 nonallergic subjects was sensitized with serial dilutions of serum containing ragweed reagins. Twenty-four or forty-eight hours later pollen was administered orally, either as whole pollen in capsules or in water or in the form of extracts. The doses varied from 15 mg. in the earlier experiments to 5,000 mg. in later trials. When no

9 Bernstein, C., Jr., and Kirsner, J. B. Oral Pollen Therapy, *J. Allergy* 8:221 (March) 1937.

10 Feinberg, S. M., and Bernstein, T. B. A Method of Measuring Rate and Degree of Absorption of Antigens, *J. Allergy* 8:523 (Sept.) 1937.

reactions occurred in the sensitized arm, a subcutaneous injection of 1 cc of a 1:66 (15 mg) dilution of the extract was administered, usually on the following day. In some instances the technique was varied by sensitizing the opposite arm with the same serum several days after the oral administration of pollen and by testing the effect of a dose given subcutaneously in both arms.

Comment—The results are recorded in table 1. After the subcutaneous injection of 15 mg of pollen, reactions occurred in sensitized areas in all the cases in sites ranging from the fourth to the seventh (serum dilutions of 1:8 to 1:64). With oral administration, all except 1 patient

TABLE 1—Results of Oral and Subcutaneous Administration of Pollen to Passively Sensitized Subjects

Case No	Ragweed Material Given Orally	Reaction	Highest Site Reacting to 1 Cc of 1:66 Subcutaneously	Serum Dilution	Factor*
1	1 cc of 1:66	0	4	1:8	8+
2	1 cc of 1:66	0	5	1:16	16+
3	5 cc of 1:66	0	4	1:8	40+
4	2.5 cc of 1:33	0	5	1:16	80+
5	15 cc of 1:33	0	5	1:16	480+
6	10 cc of 1:66 30 cc of 1:33	0 0	} Not tested subcutaneously (left hospital)		
7	Pollen, 1 Gm	1:32	4	1:8	17
8	30 cc of 1:33	0	6	1:32	1,020+
9	Pollen, 1 Gm	0	6	1:32	1,020+
10	30 cc of 1:33	0	6	1:32	1,020—
11	Pollen, 5 Gm	0	5	1:16	4,800+
12	30 cc of 1:33	0	7	1:64	3,840+
13	Pollen, 5 Gm	0	5	1:16	4,800—
14	30 cc of 1:33	0	7	1:64	3,840+
15	Pollen, 1 Gm	0	7	1:64	3,840+
16	Pollen, 1 Gm 30 cc of 1:33	0	5	1:16	1,020+
17	Pollen, 1 Gm, 30 cc of 1:33	0	Not tested subcutaneously (left hospital)		

$$* \text{ Factor} = \frac{\text{Oral dose} - \text{highest dilution of reagin}}{\text{Subcutaneous dose} - \text{highest dilution of reagin}}$$

failed to show reactions of the sensitized areas. The subject showing reactions obtained them with the serum dilution as high as 1:32 while with the subcutaneous injection he showed a reaction in the site of injection of the 1:8 dilution. (This subject had a bleeding gastric carcinoma, and it is barely possible that some of the ingested material gained direct entrance to the circulation by way of open vessels.) By dividing the subcutaneous dose by the highest dilution of the reagin at which a reaction was obtained and by comparing the latter figure with the figure obtained in the same way by oral administration, a factor was computed which is recorded in the table for each subject. This factor represents, subject to the experimental conditions, the minimal relative amounts of pollen to be taken orally in order to obtain the same amount of circulating antigen as is obtained by hypodermic administration. The figures range as high as 4,800 times. Since in all instances except 1, no reactions were obtained, the factor may well be above that in some cases.

The criticism may be offered that even though no visible reactions occur at the sensitized sites after oral administration, neutralization or desensitization of those areas may still take place. To settle this question, the following experiments were made on 6 nonallergic subjects. The left arm was sensitized as in previous experiments. Ragweed pollen (maximum dose of 5 Gm) was given orally. No reactions occurred. Several days later the right arm was sensitized with the same serum. On the following day the standard dose (1 cc of 1:66 dilution) of pollen was given subcutaneously. In every instance the first reaction (in the left arm) was at least as rapid as that in the right arm, and the height of the reaction was not exceeded in the right arm. This constitutes definite evidence of a lack of invisible desensitization by oral administration.

EXPERIMENTS ON ORAL POLLEN THERAPY

Twenty patients allergic to ragweed were given oral pollen therapy. Of these, 11 had had no pollen therapy prior to 1937, and 8 had had no pollen therapy during 1937. Of the 12 patients who had had hypodermic pollen therapy during 1937, only 1 had had sufficient treatment to lead us to expect satisfactory results. Oral therapy was given after the patient showed symptoms on presenting himself. The duration of treatment was from one to three weeks. In determining the strength of the initial doses we had in mind the relation of the oral to the hypodermic dose, as shown in the experiments described earlier in the paper. One drop of a 1:33 extract of ragweed pollen was regarded as a probably safe initial dose, since it is about 450 times the strength of the first dose (0.05 cc of a 1:10,000 extract) usually given hypodermically. The doses were given three times daily well diluted. In most instances the maximum dose was 10 to 15 drops at the end of a week. In 2 cases a maximum dose of 30 drops was used.

Comment—Table 2 indicates the results and other data concerning these patients. In 18 cases no benefit whatever was apparent with regard to the symptoms of hay fever and asthma. In 2 cases (cases 14 and 19) there was moderate improvement. In 1 of these 2 (case 14), while there was some improvement in the hay fever, there was no improvement in the asthma. In other words, there was no amelioration of the asthma in any instance. Attention should be called to the fact that in evaluating results we took into consideration the type of days encountered and the degree of suffering reported by the general group of patients with hay fever. Without such a yardstick, as one of us (S. M. F.)¹¹ has previously emphasized, therapeutic results in hay fever can hardly be considered seriously.

In 6 cases the pollen extract caused marked gastrointestinal disturbances, consisting mainly of colicky abdominal pain and nausea. One patient failed to follow directions and ingested the extract several times without diluting it. This resulted in sore throat and inability to swallow.

¹¹ Feinberg, S. M. A Method of Evaluation of Results in Hay Fever. Its Application to Certain Modes of Treatment, *Ann Int Med* 6:1153 (March) 1933.

TABLE 2—Analysis of Data for Twenty Patients Receiving Oral Pollen Therapy

Case No	Age	Sex	Diagnosis*	Duration, Years	Hypodermic Pollen Therapy			Oral Pollen Therapy in 1937 Ragweed Season			Reactions
					Prior to 1937	Results	In 1937, Maximum Dose, Pollen Units	Doses, Drops of Ragweed Extract 1/33	Period of Treatment	Improvement	
1	62	F	HF & A	10	Slight	Partial	700	1 10	9/11 9/18	None	
2	39	F	HF & A	10	0		0	1 10	9/11 9/18	None	
3	35	F	HF & A	7	0		150	1 10	8/28-9/11	None	
4	19	M	HF & A	7	1935, 1936	Good	20	1 30	8/14 9/1	None	
5	50	M	HF & A	40	1933, 1934	Fair	40	1 10	8/28-9/11	None	
6	32	M	HF & A	6	0		20	1-5	8/21 8/28	None	5 drops increased hay fever (?)
7	32	F	HF & A	12	1933	Poor	40	1-10	8/14 8/29	None (intradermal injections helped)	Cramps
8	49	F	HF & A	1	0		0	1-5	9/4 9/18	None	
9	3	M	HF & A	1	0		0	1 10	8/21 9/11	None	
10	57	F	HF & A	17	0		40	1 15	8/24 8/28	None	Nausea and cramps after 15 drops
11	20	F	HF	11	1936	Good	150	1 10	8/14 8/24	None	Nausea and cramps
12	44	M	HF & A	1	0		0	1 5	8/28 9/18	None	
13	43	F	HF & A	9	0		150	1 10	8/14 8/21	None	
14	45	F	HF & A	3	0		0	2 15	8/14 8/31	Slight for hay fever none for asthma	
15	25	M	HF & A	16	0		400	1 10	8/21 8/23	None	
16	37	F	HF & A	3	0		250	1 10	8/28 9/4	None	Nausea and cramps after 3 drops
17	8	M	HF	3	1936	Good	0	1 10	8/21 9/4	None	Nausea and cramps
18	34	M	HF	5	1935, 1936	Fair	5,000	1 30	8/18 9/4	None	
19	42	M	HF	8	1933, 1935	Good	0	1 15	8/18 8/28	Moderate	
20	30	M	HF	10	1935	Poor	0	1 10	8/25-9/4	None	Nausea and cramps

* HF indicates hay fever, and A, asthma

food for several hours subsequently. Apparently there was a local reaction in the esophagus. One patient thought that the oral therapy increased his hay fever. Any possible increase in hay fever symptoms could not be definitely ascertained in this case or in the others because of the previous existence of active symptoms. To determine this effect, preseasonal oral therapy will probably have to be tried.

COMMENT

It may be argued that the doses used were not therapeutically adequate. We are inclined to believe that such is the case, in view of our experimental results and since in the group of patients with hay fever absorption of the antigen may be even less than in the nonallergic subjects. However, there is a definite obstacle to the use of much larger doses, *i. e.*, the tendency for marked local reaction in the gastrointestinal tract. Furthermore, the variability of enteral absorption tends to lead occasionally to marked overdosage. Criticism can be leveled at our experimental work because it was done on nonallergic subjects. It should be remembered, however, that in other experiments in the past it has been found that the allergic subject shows even more diminished absorption than the nonallergic subject. Again, our previous experiments¹⁰ and present control experiments on hypodermic absorption were done on nonallergic subjects.

Perhaps a serious objection to our report is that all the therapeutic work was done coseasonally. We admit that with a long-continued pre-seasonal method of oral administration of pollen the results might have been different. We believe, however, that our work compares favorably with that of others, since coseasonal therapy was studied in most of them. Our lack of successful results may possibly be due to the difficulties encountered in desensitizing patients with ragweed sensitivity as compared with those encountered in desensitizing patients with other types of pollinosis. We realize that our group of cases is a small one, but we believe that the close study of the patients, coupled with the experimental work on absorption, makes the interpretation of our results of significance.

The disadvantages of hypodermic therapy, to which attention is called earlier in the paper, seem to apply almost as well to oral therapy. From our experience we doubt whether the average sufferer from hay fever would consider the discomfort of a gastrointestinal reaction less than that of the hypodermic needle. The total cost of frequently administered large doses orally would probably be greater than the physician's fee for a course of hypodermic injections. The question of constitutional reactions cannot be determined at this time, and we therefore cannot argue that point.

SUMMARY

A group of 20 patients with ragweed hay fever and asthma were given oral doses of pollen extracts, beginning with 1 drop of a 1:33 dilution and reaching a maximum of 10 to 30 drops three times daily. Eighteen were not benefited and 2 obtained moderate benefit. Gastrointestinal complaints were common. Experiments on absorption of ragweed pollen or extract administered orally to nonallergic subjects indicate that the amount of the antigen reaching the circulation in a unit of time is not more than about one four thousandth of the amount demonstrated in the circulation after hypodermic administration. We are justified in the conclusion that in ragweed hay fever in the Middle West, coseasonal oral pollen therapy is of little value.

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Progress in Internal Medicine

INFECTIOUS DISEASES

REVIEW OF CURRENT LITERATURE

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During the past year much new information was gathered concerning influenza, streptococci, chemotherapy and a number of "new" and rare diseases. The program for the control of pneumonia has widened so that many states have organized commissions and committees for the study and control of pneumonia and a national committee has been appointed by the surgeon general. It is fortunate that concerted studies are now being made on some of the most common of all human ills, namely, infections of the respiratory tract. Whatever success attends the efforts in prevention or control of colds, catarrh and influenza will automatically reduce the incidence of pneumonia, for in most cases pneumonia is preceded by a mild infection of the respiratory tract.

INFLUENZA

A report of important studies on influenza by English investigators is embodied in a monograph published by the British Medical Research Council.¹ The clinical description of influenza in patients proved to harbor the virus now believed to be the cause of the disease is similar in most respects to the description of the disease as it occurred in pandemic form in 1918-1919. A few differences were noted in recent epidemics: (1) symptoms of profound mental depression were absent, (2) relative bradycardia was not found often, (3) convalescence was rapid and (4) the leukocyte count was usually normal or slightly increased and leukopenia was uncommon. The erythrocyte sedimentation rate was seldom increased in cases of uncomplicated influenza.

Influenza manifests itself with varying degrees of severity, which may be listed in order as follows: (a) subclinical infections without symptoms, (b) "simple" influenza, (c) influenza with bronchiolitis and (d) influenza pneumonia. Although influenza can be diagnosed with

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¹ Stuart-Harris, C. H., Andrewes, C. H., Smith, W., Chalmers, D. K. M., Cowen, E. G. H., and Hughes, D. L. A Study of Epidemic Influenza, with Special Reference to the 1936-1937 Epidemic, Medical Research Council, Special Report Series, no. 228, London, His Majesty's Stationery Office, 1938.

certainly only when the virus is recovered, the authors attempt to separate influenza from other infections of the respiratory tract, such as "febrile catarrh," simple coryza, pharyngitis and streptococcic tonsillitis, and give the following summary of features to assist in a clinical differentiation

I EPIDEMIC INFLUENZA

1 *History*—Onset is sudden without premonitory symptoms. The first symptoms are general or constitutional, comprising headache, shivering, muscular pains and dizziness. Respiratory symptoms develop later with coryza, sore throat and cough.

2 *Course of the fever*—Rapid rise of temperature on the second day of illness may or may not be followed by a remission of temperature on the third day, but there is usually renewed pyrexia on the fourth day. General symptoms continue to dominate the illness but a short cough with but slight expectoration is more prominent during the later stages.

3 *General aspect*—The typical facies is heavy and drowsy with drooping eyelids, glistening eyes, dusky facial flush and slightly cyanosed lips.

4 *Physical signs*—These are, obstructed nose, furred tongue, husky but not hoarse voice, the signs of pharyngitis. The particular characteristics of the pharyngitis are its posterior position, its large-vessel injection, a tendency to dryness, and a granular appearance. Signs in the chest comprise rhonchi or a few rales at the bases towards the end of the fever.

5 *Complications*—Chest complications predominate over all others with a characteristic picture of "bronchiolitis," and a range of pneumonic conditions also characteristic clinically. Pneumococcal complications are common. Sinusitis occurs chiefly as a late sequela.

6 *Variations*—On the whole cases are remarkably uniform in clinical appearance and there is no tendency to admixture with other diseases such as tonsillitis. The most important variation from the typical case is the case with chest complications.

7 *Characteristics of epidemic*—The epidemic appears suddenly, rises rapidly to a peak and disappears within about 2 weeks if the population is a closed one.

II "FEBRILE CATARRHS"

In contrast with the features described above as characteristic of epidemic influenza, the catarrhal conditions which were studied in the Woolwich and Chatham (November) epidemics showed the following characteristics.

1 *History*—Onset is insidious with premonitory "cold" and cough for several days. Respiratory symptoms usher in the disease and sore throat and cough dominate the picture. Cough is paroxysmal, irritating and painful, with sub-sternal soreness over the trachea. Expectoration varies greatly, being sometimes profuse. Hoarseness of the voice develops.

2 *Course*—General symptoms of illness are overshadowed at the onset but are present during the fever with headache and muscular pains. The fever has no characteristic course and shows no special tendency to be diphasic in type.

3 *General aspect*—Often that of a patient with a heavy cold, or with brightly flushed face, injected conjunctivae and slightly cyanosed lips.

4 *Physical signs*—These are obstructed nose, clean or furred tongue, hoarse voice, and signs of tonsillitis or pharyngitis. Signs of tonsillitis are involvement

of the anterior as well as the posterior part of the fauces, intense capillary injection, and exudation of mucous, mucopurulent or follicular material. Signs in the chest are absent usually but rhonchi may be heard.

5 *Complications*—Chest complications are commoner than others and comprise bronchitis of large or small tubes, or bronchopneumonia. The haemolytic streptococcus is a common incitant of the chest complications.

6 *Variations*—The clinical picture varies greatly with alternation of the pharyngo-laryngo-tracheitis syndrome and frank tonsillitis, liable to be confused with follicular streptococcal tonsillitis.

7 *Characteristics of epidemic*—Gradual development from the basal respiratory disease of the population (coryza and tonsillitis). Slow rise and fall with prolonged duration of epidemic over several weeks.

In tabular form the essential clinical features are contrasted as follows:²

	Epidemic Influenza	Febrile Catarrhs
Onset	Sudden	Insidious
Symptoms	Constitutional symptoms predominate	Respiratory symptoms predominate
Cough	Short and dry	Paroxysmal, irritating, painful, often productive
Voice	Husky	Hoarse
Throat	Posterior pharyngitis, no exudate	Tonsillitis as well as pharyngitis, exudate common
Fever	Sometimes diphasic	Rarely diphasic
Complications	Bronchiolitis and pneumonia	Bronchitis or bronchopneumonia
Epidemic	Short with rapid "peaking"	Prolonged and "grumbling"
Contacts	Clinical picture uniform, although graded in severity	Clinical picture variable with frank tonsillitis in contacts
Leukocyte count	Not diagnostic	Not diagnostic
Virus	Influenza virus recoverable from pharynx	Influenza virus not concerned

The monograph contains a detailed report of experiments with the use of vaccine and of specific immune serum in the prevention and treatment of influenza. Vaccine increased the specific immune bodies in the blood strikingly, even to some extent against influenza viruses slightly different serologically from the strain used as the antigen. The experiments are also described in a separate publication by Andrewes.³ He asserts that contrary to much opinion, a virus vaccine killed with formaldehyde is as effective an antigen as a living one. Difficulty was encountered in preparing a vaccine free from undesirable protein material. He vaccinated several groups of volunteers with virus inactivated with solution of formaldehyde and succeeded in increasing the antibodies against influenza in the blood. The antibodies reached their height in about a fortnight. It was disappointing that in several persons thus vaccinated influenza developed, which indicates that the vac-

² Stuart-Harris, C. H. Epidemic Influenza, Brit. M. J. 2 516-518 (Sept. 11) 1937.

³ Andrewes, C. H. Influenza. Four Years' Progress, Brit. M. J. 2 513-515 (Sept. 11) 1937.

cine is not as yet reliable. The results obtained by treating patients with immune horse serum were not convincing, but the severity of the infection in mice was definitely lessened even if the serum was injected on the first or the second day of the disease.

Francis and his co-workers⁴ studied an epidemic of disease of the respiratory tract in the winter of 1936-1937. The washings from the throat in 52 of 100 cases contained the virus of epidemic influenza. In 48 cases a diagnosis of influenza was made on the basis of neutralization tests and the complement fixation reaction. By using the same procedures, numbers of patients with infection of the respiratory tract were found during the epidemic whose disease was caused by some agent other than the influenza virus. The authors emphasize the importance of persons who have mild or subclinical infections as disseminators of infection. Mild or subclinical infections probably account for the frequency with which evidence of immunity is found in the apparent absence of a preceding attack of influenza.

Two British investigators⁵ were successful in vaccinating mice against influenza by using heat-killed suspensions of "elementary bodies" of influenza virus. These bodies were obtained by differential centrifugation and were believed by the authors to contain the immunogenic fraction of influenza virus. Less success attended the immunization of ferrets, but since large doses of viruses were necessary to infect these animals the authors are still optimistic about the success of the vaccine if given to human beings.

Neal and Wilcox⁶ studied a number of patients who supposedly had influenza and in whom encephalitis later developed to find whether the two conditions were etiologically related. In several cases no evidence was found to confirm a diagnosis of influenza. It is also known that animals experimentally infected with influenza virus do not show nervous symptoms, and in many outbreaks of influenza, encephalitis does not occur, both facts fail to support any relation between the two. It is unknown whether certain acute infections of the respiratory tract permit the invasion of an agent which causes encephalitis or whether the first symptoms of encephalitis itself are manifested in the respiratory tract. Hamburger⁷ discusses various opinions concerning the effect

4 Francis, T., Magill, T. P., Rickard, E. R., and Beck, M. D. Etiological and Serological Studies in Epidemic Influenza, *Am J Pub Health* **27** 1141-1159 (Nov) 1937.

5 Fairbrother, R. W., and Hoyle, L. Active Immunization Against Experimental Influenza. Use of Heat-Killed Elementary Body Suspensions, *Brit J Exper Path* **18** 430-435 (Dec) 1937.

6 Neal, J. B., and Wilcox, H. L. Does the Virus of Influenza Cause Neurological Manifestations? *Science* **86** 267-268 (Sept 17) 1937.

7 Hamburger, W. W. The Heart in Influenza, *M Clin North America* **22** 111-121 (Jan) 1938.

of influenza on the heart. It seems that influenza is not a frequent cause of heart disease, yet in a certain number of patients evidence of disorder of the circulatory system is present.

The detection of an epizootic virus disease of ferrets by Slanetz and Smetana⁸ must serve as a warning to those who employ these animals for the diagnosis of influenza. The clinical course of the infection resembles the disease caused by the inoculation of ferrets with human influenza virus, but there seems to be no immunologic relation between the viruses of ferret disease, of human influenza and of canine distemper.

Influenza Pneumonia.—Several studies based on the newly discovered virus of influenza seem to clarify a number of problems concerning influenza pneumonia. Straub⁹ studied the lungs of mice infected with the virus and found necrobiosis and fibroid necrosis of the epithelium of the respiratory and terminal bronchioles leading to complete desquamation. There were secondary dilation of the bronchioles and collapse of the alveoli, with edema and hyperemia. The cellular reaction was chiefly of the mononuclear type of cell. The lesions as described were strikingly like those reported by MacCallum, Goodpasture and others in human beings in the 1918-1919 pandemic, at which time a number of observers suggested that a virus may be operative. Snow and Cassasa¹⁰ note the frequency with which emphysema and atelectasis occur in human beings with influenza. Scadding¹¹ reports a study of 58 patients with influenza. Of these patients, 18 gave no evidence of pulmonary involvement, in 21 there were physical signs of congestion and in 19 there was evidence of consolidation. Seven of the last-mentioned group died. Bacteriologic study of the sputum showed no special variety of bacteria to be present. Pneumococci generally predominated in the patients who had pneumonia. In 1 case the staphylococcus alone was operative. Scadding believes that the findings in his cases were essentially the same as those reported in 1918-1919.

It seems that heretofore three forms of pulmonary infection have been called influenza pneumonia. The first is caused by the virus of influenza itself and perhaps represents the most severe form of the disease, the second is caused by the influenza bacillus of Pfeiffer and the third is caused by a variety of bacteria, either as single species

8 Slanetz, C. A., and Smetana, H. An Epizootic Disease of Ferrets Caused by a Filterable Virus, *J. Exper. Med.* **66** 653-666 (Dec.) 1937.

9 Straub, M. The Microscopical Changes in the Lungs of Mice Infected with Influenza Virus, *J. Path. & Bact.* **45** 75-78 (July) 1937.

10 Snow, W., and Cassasa, C. S. B. Obstructive Emphysema and Atelectasis in Influenza, *J. A. M. A.* **109** 1886-1888 (Dec. 4) 1937.

11 Scadding, J. G. Lung Changes in Influenza, *Quart. J. Med.* **6** 425-466 (Oct.) 1937.

or in mixtures, invasion being made possible by the harmful action of the virus of influenza on the lung or by the shocklike reaction in cases of severe influenza. Pneumonia in influenza may therefore be caused in at least two ways. First, a specific lesion caused by influenza virus itself may be secondarily invaded by other bacteria, second, pneumonia may occur as the result of severe systemic infection with circulatory failure and a shocklike condition during which the lungs are susceptible to infection with any or all of a mixture of bacteria which happen to be present in the respiratory tract. Recent studies have suggested a similar state of affairs regarding the virus diseases measles, vaccinia and psittacosis.

Haemophilus Influenzae Meningitis—Fothergill¹² reports slight success in the treatment of meningitis caused by Pfeiffer's bacillus with specific immune serum. The mortality of untreated patients is nearly 100 per cent, it appeared to be reduced to 84 per cent by serum treatment. In the years between 1933 and 1936 the following specific forms of meningitis were encountered among children:

Organism	No. of Cases
<i>Haemophilus influenzae</i>	51
<i>Pneumococcus</i>	38
<i>Streptococcus haemolyticus</i>	36
<i>Tubercle bacillus</i>	31
<i>Meningococcus</i>	27
Others	38

The incidence of the influenza bacillus as a cause of meningitis is surprisingly large.

PNEUMONIA AND THE PNEUMOCOCCUS

Perhaps the most important development in the field of pneumonia during the past year is the organization of committees or commissions in many states and cities for its study and control and finally the appointment of a national committee by the surgeon general. As pointed out by Cole¹³ in a recent paper, physicians acting individually or in small groups have not been effective in controlling such epidemic diseases as tuberculosis, diphtheria and smallpox unless assisted by public health organizations. To popularize new methods for the control or treatment of pneumonia or of any epidemic disease, it is necessary to provide for the instruction of physicians generally, particularly of those who have been in practice for many years. In addition, the difficulties

¹² Fothergill, L. D. *Haemophilus Influenzae (Pfeiffer Bacillus) Meningitis and Its Specific Treatment*, New England J. Med. **216**: 587-590 (April 8) 1937.

¹³ Cole, R. Possibilities for Pneumonia Control as Indicated by Present Scientific Knowledge, Mil. Surgeon **81**: 241-255 (Oct.) 1937.

of typing pneumococci in sputum must be minimized by the establishment of reliable laboratories in convenient places, physicians must be taught when to use antipneumococcus serum, how to obtain it and how to use it. These services can best be rendered by public health agencies. In many states typing of pneumococci is performed free, and serum is supplied free to those patients who cannot afford to buy it or to those who find it a hardship to pay for it.

Further report is made on the treatment of pneumococcic pneumonia with unconcentrated rabbit serum at the Hospital of the Rockefeller Institute¹⁴. Among 54 patients with pneumonia caused by 8 types of pneumococci, I, II, V, VI, VII, VIII, XIV and XVIII, only 2 deaths occurred, a mortality rate of 3.7 per cent. One of the striking features noted was the rapid recovery of most patients, the average interval from the beginning of treatment with serum until the disappearance of signs of acute illness was only twenty-seven hours. In 18 cases in which the full therapeutic dose was given in a single injection, the interval between the beginning of therapy and the crisis was about eight hours. Good results were not obtained from the serum treatment of 13 patients with pneumonia due to type III pneumococci. Six of these patients died.

An unexpected disadvantage in the use of type XIV antipneumococcus horse serum was discovered by Finland and Curnen¹⁵. Because serious and fatal reactions were noted to occur in patients treated with serum, attempts were made to find the reason. It was discovered that each of the different samples of type XIV antipneumococcus serum tested agglutinated human erythrocytes of all four blood groups. Other types of antipneumococcus horse serum were also tested, but only 2 agglutinated erythrocytes in low dilution. When type XIV antiserum was absorbed with type XIV pneumococci, agglutinins for the pneumococci and for the erythrocytes were removed, absorption with erythrocytes removed agglutinins for erythrocytes but not for the pneumococci. A number of antipneumococcus rabbit serums prepared with the same strains of type XIV pneumococci used in preparing horse serum were tested, but none agglutinated human erythrocytes in high titer.

Attempts were made¹⁶ to test the effect of high temperature in the treatment of infection due to type III pneumococci. Previous experi-

14 Horsfall, F. L., Goodner, K., and MacLeod, C. M. Antipneumococcus Rabbit Serum as a Therapeutic Agent in Lobar Pneumonia, *New York State J. Med.* **38** 245-255 (Feb. 15) 1938.

15 Finland, M., and Curnen, E. C. Agglutinins for Human Erythrocytes in Type XIV Antipneumococcus Horse Serums, *Science* **87** 417-418 (May 6) 1938.

16 Shaffer, M. F., Enders, J. F., and Wilson, J. The Effect of Artificial Fever and Specific Antiserum on the Organisms Present in Cases of Type III Pneumococcus Meningitis, *J. Clin. Investigation* **17** 133-145 (March) 1938.

ments with rabbits had led to the belief that they are immune to infection with certain strains of type III pneumococci which fail to grow at a temperature over 105 F because the temperatures of rabbits after infection often exceeded this level. Accordingly, the body temperature of 2 patients with meningitis due to type III pneumococci was raised artificially to 105 F or higher for several hours. After this treatment the number of pneumococci in the spinal fluid was markedly reduced, but in neither case was the fluid sterilized. Two other patients were given injections of type III antipneumococcus rabbit serum intraspinally. Temporary sterility was accomplished in both cases, but pneumococci later reappeared. In 1 case, combined fever therapy and antipneumococcus serum failed to prevent death.

In experimental studies of pneumococcic pneumonia in dogs, Robertson¹⁷ made further important contributions in regard to the problem of immunity. Dogs were actively and passively immunized by the injection of large amounts of specific antipneumococcus horse serum and by vaccination with living and dead pneumococci. Neither the passive nor the active immunity thus produced served to protect the dogs regularly against pneumonia when pneumococci were injected deep into the lungs according to the author's method. The resulting lesion in the lung was often less in extent, and the disease produced was of shorter duration, than that in immunized dogs. The combination of active and passive immunization was better than one or the other alone, but the greatest protection was attained only when the infective dose of pneumococci and the specific immune serum were injected at the same time. The experiments are not encouraging as far as the ultimate practical application of vaccine prophylaxis against pneumonia in man is concerned.

Studies are constantly under way to test the efficiency of different forms of treatment for pneumonia, notably by diathermy and roentgen irradiation. In regard to diathermy, Coulter¹⁸ states that there is no evidence to show its effectiveness in treating patients with pneumonia except as a counterirritant to relieve pleuritic pain. Another paper¹⁹ deals with roentgen therapy of lobar pneumonia. The results described are unconvincing and cannot be accepted as showing the value of this

17 Robertson, O. H. The Effect of Increased Antipneumococcal Immunity on the Inception of Experimental Lobar Pneumonia in the Dog, *J. Exper. Med.* **66** 705-727 (Dec.) 1937.

18 Coulter, J. S. Medical Diathermy in Pneumonia, *M. Clin. North America* **22** 61-68 (Jan.) 1938.

19 Powell, E. V. Roentgen Therapy of Lobar Pneumonia, *J. A. M. A.* **110** 19-22 (Jan. 1) 1938.

form of treatment Whenever an author reports a mortality rate of from 25 to 4 per cent in a large number of cases of pneumonia after the first day or two of treatment by any method, two conclusions are possible first, that a marvelous new remedy is at hand or, second, that the diagnoses are not in accord with those of most clinicians, since practically all studies have shown that the mortality rate for patients with pneumonia untreated with specific immune serum varies between 30 and 40 per cent Accurate experimental studies on the effect of roentgen rays on pneumococcic infections are urgently needed

A new form of vaccine against pneumococcic pneumonia prepared with fractions of the pneumococcus body is being tested on a large scale by Felton Thousands of persons have been vaccinated, and other thousands under similar environmental conditions are being observed as controls The studies made thus far are not sufficiently advanced to permit a statement of the effect obtained by vaccination in preventing pneumonia

Lindqvist²⁰ studied the vitamin A content of the serum of patients with pneumonia Carotenoid and vitamin A were low in amount during the disease, but during convalescence the amount increased rapidly without the addition of the vitamin to the diet During fever large quantities escaped in the urine One week after the crisis the vitamin content was three times as high as it was at the lowest point There is no evidence to show that the administration of vitamin A during pneumonia has any effect on the disease

Dick and Boor²¹ report the isolation of a toxin or toxin-like substance produced by autolysis of pneumococci which seems to produce a weak antitoxin It is questionable if this substance is not the same as the purpura-producing substance obtained by autolysis of pneumococci, as reported by many other investigators

Because most deaths of children with nephrosis are caused by pneumococcic peritonitis, MacLeod and Farr²² studied the relationship of types of pneumococci carried in the nasopharynx of children with nephrosis to determine whether the infection was exogenous (contracted from outside sources) or endogenous (arising from the invasion of bacteria carried in the nasopharynx) In each of 6 children studied, the same type of pneumococcus was recovered from the throat as from

20 Lindqvist, T Untersuchungen uber das Vitamin A bei Pneumonie, *Klin Wchnschr* **16** 1345-1347 (Sept 25) 1937

21 Dick, G F, and Boor, A K Pneumococcus Toxin and Antitoxin, *J Infect Dis* **61** 228-233 (Sept-Oct) 1937

22 MacLeod, C M, and Farr, L E Relation of the Carrier State to Pneumococcal Peritonitis in Young Children with the Nephrotic Syndrome, *Proc Soc Exper Biol & Med* **37** 556-557 (Dec) 1937

the pus in the abdomen, suggesting that invasion occurred with the types habitually present. Types VI, X, XIX, XX and XXVIII were found.

Pickrell,²³ in following up previous work of Stillman and others, tested the effect of alcohol in reducing the resistance of rabbits to pneumococcal infection. Alcoholic intoxication was found to destroy resistance to pneumococci even in animals rendered highly immune by vaccination. The loss of resistance was presumably due to inhibition of the vascular inflammatory response as a result of intoxication. Leukocytic immigration to the site of infection was negligible, and the bacteria grew unhampered. Ether anesthesia had a similar inhibitory effect on the inflammatory response.

Moon^{23a} studied the origin and pathology of what is perhaps the most common form of pneumonia, namely, that form called terminal pneumonia. Congestion, stasis and edema, which, he believes, constitute the essential pathologic features of shock, are the chief factors in the causation of this form of pneumonia.

The publication of White's²⁴ review dealing with practically all the published papers concerning the biology of the pneumococcus must be regarded as a notable achievement. In this comprehensive and critical survey, 1,593 papers are surveyed, and the subject is brought together in a clear, logical and unified treatise which for many years should be a source of stimulation for those interested in infectious disease and pneumonia. The pages fairly bristle with suggestions for attack on unsolved problems. It is of interest to speculate on the amount of time which has thus far been devoted to research on the pneumococcus. If, for example, each of the papers listed represents an average of three months of work, one could hazard an estimate that about four hundred years has been spent on the investigation of this amazing cell.

STREPTOCOCCI AND STREPTOCOCCIC INFECTIONS

Bradley²⁵ made a study concerning the epidemiology of infections due to hemolytic streptococci. About 20 per cent of a group of patients in one hospital were found to be carriers of hemolytic streptococci,

23 Pickrell, K. L. *Effect of Alcoholic Intoxication and Ether Anesthesia on Resistance to Pneumococcal Infection*, Proc Soc Exper Biol & Med **38** 265-267 (March) 1938.

23a Moon, V. H. *Origin and Pathology of Common Terminal Pneumonia*, Arch Path **26** 132-143 (July) 1938.

24 White, B., Robinson, E. S., and Barnes, L. A. *The Biology of Pneumococcus*, New York, Commonwealth Fund, Division of Publications, 1938.

25 Bradley, W. H. *Epidemiology of Streptococcal Infections*, Guv's Hosp Rep **87** 372-390 (July) 1937.

most of which, according to Griffith's classification, were of the types potentially pathogenic for man. The distribution of types was as follows

Type	No of Cases	Type	No of Cases	Type	No of Cases
I	3	IX	3	XVIII	4
II	2	X	1	XXI	7
III	1	XI	3	XXII	11
IV	16	XIII	9	XXV	1
V	7	XV	3	XXVI	1
VI	1	XVI	5	XXVII	1
VII	1	XVII	1	XXVIII	3

Most of the patients examined were transient carriers, usually for only a few days, but a number of them persistently carried the streptococci. In several examples of epidemics of hemolytic streptococcal infections in families, a single type was involved and was sometimes found in all exposed persons. Overcrowding and uncleanness favored the appearance of many carriers in a group. The author regards acute tonsillitis due to hemolytic streptococci as a dangerous infection which equals diphtheria in epidemiologic significance. It is perhaps not generally realized that bacteria in the dry state may float about in the air much as does tobacco smoke (Wells).

Shaw²⁶ also studied the types of hemolytic streptococci found in patients. Streptococci of Lancefield's group A were present in 90 per cent of infections in human beings, in 1 case, a streptococcus of group C was present and in another a streptococcus of group G. Type II and type XXV streptococci were most frequently found in cases of puerperal infection, types IV, VI, VIII and XXII were also often present. Among 29 strains of streptococci found in the nasopharynxes of normal persons, 9 were of group A, 1 was of group B and 1 was of group C. Eighteen of the strains failed to form soluble hemolysin and could not be classified.

Smith and Sherman²⁷ studied 109 cultures of hemolytic streptococci isolated from 45 samples of human feces. Streptococci of Lancefield's group A were not encountered. The streptococci most commonly found were those of group D and a related "enterococcus," *Streptococcus durans*. Members of groups B, C, F and G were also found.

Long and Bliss²⁸ studied the incidence of minute beta hemolytic streptococci and ordinary beta hemolytic streptococci in the flora of the throats of healthy and of diseased persons. The incidences of the two varieties in healthy persons were about the same (12 per cent),

²⁶ Shaw, C. Serological Group and Typing of Hemolytic Streptococci, *Lancet* 2 1193-1194 (Nov 20) 1937.

²⁷ Smith, F. R., and Sherman, J. M. The Hemolytic Streptococci of Human Feces, *J. Infect. Dis.* 62 186-189 (March-April) 1938.

²⁸ Long, P. H., and Bliss, E. A. Studies upon Minute Hemolytic Streptococci, *J. Infect. Dis.* 62 52-57 (Jan-Feb) 1938.

but when cultures were made repeatedly, the incidence of the ordinary type increased considerably more than that for the minute forms. In persons with rhinitis or infections of the upper respiratory tract the incidence of both forms of streptococci was lower than usual. Children whose tonsils had not been removed "showed a definitely higher subject incidence for both groups" of streptococci. The minute beta hemolytic streptococcus was seldom found in patients with chronic disease, scarlet fever or streptococcic tonsillitis. Minute forms, however, were present in 55 per cent of the patients with rheumatic fever or its sequelae and in 96 per cent of 48 patients with diffuse glomerular nephritis.

In experimental studies,²⁹ hemolytic streptococci were injected into the paranasal sinuses of cats and rabbits and were traced to their deposition in the lungs. The fact that streptococci were found in the lungs, liver and spleen indicates that the anatomic pathway from the sinuses must be through the paralaryngeal and paratracheal lymph nodes and lymph vessels to the great veins which empty into the right auricle and that from there the organisms are carried by the blood to the lungs and elsewhere. The passage of infection from the sinuses by way of direct lymphatic connection to the lungs is rather unlikely, since the lymphatic chains are frequently interrupted by lymph nodes.

Dawson and his associates³⁰ report the existence of a scheme of bacterial variation among hemolytic streptococci which closely resembles the well known M, S and R forms of pneumococci and other bacteria. The capsular polysaccharide substance of the mucoid (M) forms of group A streptococci, unlike that of the pneumococcus, is not type specific.

After an uncritical and poorly controlled study Rosenow and Heilman³¹ report favorable results in the prevention and treatment of colds and influenza by the use of vaccines made from a mixture of 400 strains of streptococci. No attempt was made to differentiate the cold from influenza, and no mention is made of the recent studies on the viruses of either disease or of the fact that numerous bacteria other than streptococci may secondarily invade persons ill with colds or influenza. In spite of a statement to the contrary, there is no evidence that vaccines of any kind favorably influence in a specific manner subsequent infections with streptococci. The use of vaccines in the specific treatment of any infection is illogical. One is amazed at the persistence of some

29 Larsell, O, Veazie, L, and Fenton, R. A. Streptococcus Infection of the Lung from the Paranasal Sinuses, *Arch Otolaryng* **27** 143-150 (Feb) 1938.

30 Dawson, M. H., Hobby, G. L., and Olmstead, M. Variation in the Hemolytic Streptococci, *J Infect Dis* **62** 138-168 (March-April) 1938.

31 Rosenow, E. C., and Heilman, F. R. Streptococcal Vaccines in the Prevention and Treatment of Respiratory Infections, *Am J Clin Path* **8** 17-27 (Jan) 1938.

investigators who continue to publish work so consistently at odds with the bulk of evidence, with little or no reference to work which fails to corroborate their results. If such publications did not confuse and obstruct scientific thought, they might be regarded as stimulating or at least provocative, but unfortunately they are for the most part simply misleading. There seems to be no end to the number of diverse diseases which Rosenow believes to be caused by streptococci, as indicated in the following list:

Influenza	Epidemic hiccup	Ocular diseases
Colds	Erythema nodosum	Prostatitis
Poliomyelitis	Renal stones	Myositis
Encephalitis	Chorea	Myasthenia gravis
Multiple sclerosis	Arthritis	
Herpes zoster	Rheumatic fever	
Neuritis	Epidemic gastroenteritis	
Torticollis	Appendicitis	

Schottmuller, discussing a paper read by Rosenow at the German Congress of Medicine at Wiesbaden, said that Rosenow's theory of elective localization not only must be disregarded but must be combated. Similar views were expressed by Pette.

SULFANILAMIDE

It is not within the province of this review to list all the papers published during the past year on the subject of sulfanilamide. A great many papers are reports on single patients treated with the drug, and many studies are not scientifically controlled. General reviews may be found in the papers of Long and Bliss³² and others.

Mode of Action—In Bliss and Long's³³ experiments, sulfanilamide apparently did not kill bacteria directly but seemed to inhibit the growth of hemolytic streptococci and *Clostridium welchii* both in vitro and in vivo. Temporary inhibition of growth or bacteriostasis seemed to permit the natural forces of the body to cope with the infection successfully and led to recovery. The authors tried to show the importance of the phagocytic action of the polymorphonuclear leukocytes as one of the natural forces. They injected benzene into mice, according to Rich's technic, to destroy the leukocytes before infecting the mice with streptococci and treating them with sulfanilamide. Because the mice rendered granulocytopenic died and controls recovered, the authors assume that polymorphonuclear leukocytes are required in the process of recovery. While this may be true, the experiments are open to criticism, since

32 Long, P. H., and Bliss, E. A. The Clinical Use of Sulfanilamide and Its Derivatives in the Treatment of Infectious Disease, *Ann Int Med* **11** 575-592 (Oct.) 1937.

33 Bliss, E. A., and Long, P. H. Observations on the Mode of Action of Sulfanilamide, *J A M A* **109** 1524-1527 (Nov. 6) 1937.

poisoning a mouse with benzene causes other changes in addition to reducing the number of circulating leukocytes

According to Gay and Clark,³⁴ the serum of rabbits treated with sulfanilamide inhibited the growth of streptococci in vitro. Neter³⁵ reports similar bacteriostatic effects of the drug on the meningococci present in the spinal fluid of patients with meningitis.

Finkelstein and Birkeland³⁶ conclude that the presence of serum is necessary for the drug to be effective in causing phagocytosis in vitro, the serum-sulfanilamide complex acts, therefore, as an opsonin. There seems to be no reason to confuse the matter by introducing the word opsonin. Obviously, when any drug is used to inhibit growth of bacteria, some of the bacteria will die and be taken in by phagocytes.

Osgood³⁷ and Brownlee could not demonstrate any direct effect of sulfanilamide on phagocytosis. The drug apparently decreases the rate of division of streptococci, and its major effect seemed to the authors to be the neutralization of toxins. Their conclusion is not substantiated by evidence. Huntington³⁸ was unable to show that sulfanilamide had any effect on fibrinolysis or on the formation of toxin in vivo. It also failed to inactivate small amounts of toxin.

Streptococcic Infections—Sulfanilamide exerts its beneficial effect on infections caused by hemolytic streptococci and not on those caused by *Streptococcus viridans*. Spink at a recent meeting reported long remissions in several cases of subacute bacterial endocarditis after treatment with sulfanilamide. Mellon and Cooper³⁹ call attention to certain strains of group A hemolytic streptococci which may at times cause green pigmentation on blood agar plates and may be mistaken for *Str. viridans*. The strains they studied grew in colonies surrounded by a broad grass-green zone when plated on blood agar plates at a p_H of 6, but when the same strain of streptococci was plated on blood agar at p_H 8, the hemolytic activity became dominant, and the colonies were surrounded by zones of hemolysis. The production of hemolysis or of

34 Gay, F. P., and Clark, A. R. Mode of Action of Sulfanilamide in Experimental Streptococcic Empyema, *J. Exper. Med.* **66** 535-548 (Nov.) 1937.

35 Neter, E. Bacteriostatic Action of Sulfanilamide upon Meningococcus in Spinal Fluid, *Proc. Soc. Exper. Biol. & Med.* **38** 37-40 (Feb.) 1938.

36 Finkelstein, R., and Birkeland, J. M. The Mode of Action of Sulfanilamide and Prontosil, *Science* **87** 441-442 (May 7) 1938.

37 Osgood, E. E. Culture of Human Marrow. Studies on the Mode of Action of Sulfanilamide, *J. A. M. A.* **110** 349-356 (Jan. 29) 1938.

38 Huntington, R. N. Failure of Sulfanilamide to Prevent Hemolysis, Fibrinolysis and Production of Erythrogenic Toxin by Hemolytic Streptococci in Vitro, *Proc. Soc. Exper. Biol. & Med.* **38** 328-331 (April) 1938.

39 Mellon, R. R., and Cooper, F. B. The Bi-Phasic Nature of Certain Alpha-Prime (?) Hemolytic Streptococci, *Proc. Soc. Exper. Biol. & Med.* **38** 158-160 (Feb.) 1938.

green coloration of blood agar by certain strains of hemolytic streptococci therefore depends on the environment in which the bacteria grow. If these streptococci obtained from patients successfully treated with sulfanilamide happen to be plated on mediums favoring the development of the green phase, one is likely to be misled into ascribing a curative effect of the drug for infection due to *Str. viridans*.

One also must not be misled by overenthusiastic and careless statements prepared for general readers concerning the value of various therapeutic measures, especially when they are printed in journals otherwise noted for their accuracy. In one such article⁴⁰ streptococcic meningitis untreated with sulfanilamide was said to be invariably fatal. This is not true, for several reports of recovery of patients not treated with the drug have appeared within the past year.

A number of observers⁴¹ have obtained some degree of success in treating erysipelas with sulfanilamide, but here again, one must be cautious in accepting such reports as final when one recalls the exceptionally good results claimed for the treatment of this disease with immune serum, with roentgen rays and with ultraviolet radiation. Colebrook,⁴² in one of his later papers, continues to write of satisfactory results in treating puerperal sepsis caused by hemolytic streptococci with sulfanilamide but claims that the resolution of the process seems to be less spectacular than it appeared to be in the earliest days of enthusiasm.

It was disappointing to read of the apparent ineffectiveness of sulfanilamide in the treatment of scarlet fever in Hogarth's⁴³ paper. The failure may raise some question of the actual etiologic role of hemolytic streptococci in scarlet fever, which numerous investigators have persistently doubted, or perhaps sulfanilamide has no effect on the toxins of hemolytic streptococci which may be operating from a focus safe from the effects of the drug.

Acute Rheumatic Fever—Rheumatic fever is another disease often believed to be associated with hemolytic streptococci in which sulfanilamide has no beneficial effects. In careful studies Swift, Moen and Hirst⁴⁴ were unable to shed much new light on the subject except

40 Stafford, J. Prontosil, *Science* (supp.) **85** 9-10 (June 18) 1937.

41 Snodgrass, W. R., and Anderson, T. Prontosil in Treatment of Erysipelas. Controlled Series of Three Hundred and Twelve Cases, *Brit. M. J.* **2** 101-104 (July 17) 1937. Breen, G. E., and Taylor, I. Erysipelas Treated with Prontosil, *Lancet* **1** 1334-1335 (June 5) 1937.

42 Colebrook, L., and Purdie, A. W. Treatment of One Hundred and Six Cases of Puerperal Fever by Sulphanilamide (Streptocide), *Lancet* **2** 1291-1293 (Dec. 4) 1937.

43 Hogarth, J. C. Para-Benzylaminobenzenesulphonamide in the Treatment of Scarlet Fever, *Brit. M. J.* **2** 1160-1162 (Dec. 11) 1937.

44 Swift, H. F., Moen, J. K., and Hirst, G. K. The Action of Sulfanilamide in Rheumatic Fever, *J. A. M. A.* **110** 426-434 (Feb. 5) 1938.

to discuss the possible effects of the drug on streptococci which may be harbored in the tonsils or elsewhere to serve as hypothetic foci of infection. The administration of sulfanilamide apparently has no effect on hemolytic streptococci located in the tonsils or in the lochia of women who recover from puerperal infection. Massell and Jones^{44a} also report that they have found sulfanilamide to be ineffective in influencing the course of rheumatic fever. Sulfanilamide⁴⁵ was without effect in controlling experimental infection with staphylococci. At the meeting of the Association of American Physicians held in May 1938 Bauer reported no success in the treatment of rheumatoid arthritis with sulfanilamide.

Pneumococcic Infections—Infection experimentally induced in animals with pneumococci of types I,⁴⁶ II, III⁴⁷ and XIV⁴⁸ were effectively controlled by the administration of sulfanilamide. In many of these experiments the amount of the drug that had to be given to obtain a satisfactory cure was far in excess of the amount tolerated by human beings in proportion to body weight.

Gonococcic Infections—Most reports concerning the treatment of gonorrhea with sulfanilamide have been favorable, yet the studies have often been uncontrolled, and in many cases the patients treated were not observed long enough after the supposed cure. It is still too early to judge the value of the drug for this infection. The tone of one paper, that of Johnson and Pepper,⁴⁹ is pessimistic. More than half the patients treated were not sufficiently benefited so that curative power could be ascribed to the drug. The authors do not recommend therapy with sulfanilamide as a type of treatment to be employed for ambulatory patients.

44a Massell, B. F., and Jones, T. D. Effect of Sulfanilamide on Rheumatic Fever and Chorea, *New England J. Med.* **218** 876-877 (May 26) 1938.

45 Mellon, R. R., Shinn, L. E., and McBroom, J. Therapy of Experimental Staphylococcus Infections with Sulfonamide Compounds, *Proc. Soc. Exper. Biol. & Med.* **37** 563-565 (Dec.) 1937.

46 Kreidler, W. A. Treatment of Pneumococcal Infections in Rabbits with Sulfanilamide, *Proc. Soc. Exper. Biol. & Med.* **37** 146-149 (Oct.) 1937.

47 Cooper, F. B., and Gross, P. Para-Aminobenzenesulfonamide Therapy in Experimental Type III Pneumococcal Pneumonia, *Proc. Soc. Exper. Biol. & Med.* **36** 678-681 (June) 1937, Sulfanilamide, Antipneumococcus Serum and Vitamin C Therapy in Type II Pneumococcal Pneumonia of Rats, *ibid.* **36** 774-776 (June) 1937.

48 Schmidt, L. H. Use of Sulfanilamide in the Treatment of Type XIV Pneumococcus Infections in Mice, *Proc. Soc. Exper. Biol. & Med.* **37** 205-206 (Oct.) 1937.

49 Johnson, H. S., and Pepper, S. D. The Evaluation and Danger of the Treatment of Gonorrhea with Derivatives of the Sulfonamide-Azo Dyes, *Week Roster* **33** 465 (Dec. 11) 1937.

Other Infections—Both experimental and clinical studies⁵⁰ indicate a favorable effect of sulfanilamide on infections caused by the meningococcus. A combination of immune serum and drug therapy seems most effective⁵⁰. Two English physicians⁵¹ report success in the treatment of undulant fever with sulfanilamide. In the 4 patients treated recovery occurred after the drug had been given. The effects are not wholly convincing. More striking results are reported by Stern and Blake⁵².

Rich and Follis⁵³ found sulfanilamide to have striking effects in inhibiting the development of tuberculosis in guinea pigs experimentally infected with tubercle bacilli. When the animals were given small doses (100 mg per day) the effects were not good, but when doses of 500 mg were given daily the tuberculous process was well controlled. Under somewhat different experimental conditions Smithburn^{53a} was unable to detect any influence of sulfanilamide in guinea pigs inoculated with tubercle bacilli.

Both sulfanilamide and mandelic acid appear to be of value in the treatment of infections of the urinary tract, especially if colon bacilli or hemolytic streptococci are operative⁵⁴. Sulfanilamide exerts its best effects when the urine is acid, preferably at a p_H of 5.5 or less. The drug has no value if infection is caused by group D hemolytic streptococci.

50 Branham, S. E., and Rosenthal, S. M. Studies in Chemotherapy. V. Sulfanilamide, Serum and Combined Drug and Serum Therapy in Experimental Meningococcic and Pneumococcic Infections in Mice, *Pub Health Rep* **52** 685-695 (May 28) 1937.

51 Richardson, L. A. Infection with *Brucella Abortus* Treated with Prontosil, *Lancet* **1** 495-496 (Feb 26) 1938. Francis, A. E. Sulfanilamide in the Treatment of Undulant Fever, *ibid* **1** 496-497 (Feb 26) 1938.

52 Stern, R. L., and Blake, K. W. Undulant Fever. Its Treatment with Sulfanilamide, *J. A. M. A.* **110** 1550-1551 (May 7) 1938.

53 Rich, A. R., and Follis, R. H. Inhibiting Effect of Sulfanilamide on the Development of Experimental Tuberculosis in the Guinea Pig, *Bull Johns Hopkins Hosp* **62** 77-84 (Jan) 1938.

53a Smithburn, K. C. Inefficacy of Prontylin in Experimental Tuberculosis, *Proc Soc Exper Biol & Med* **38** 574-575 (May) 1938.

54 Kenny, M., Johnston, F. D., and Von Haebler, T. *p*-Aminobenzenesulfonamide in Treatment of Bacterium *Coli* Infections of the Urinary Tract, *Lancet* **2** 119-125 (July 17) 1937. Walther, H. W. E. Urinary Antisepsis, *J. A. M. A.* **109** 999-1004 (Sept 25) 1937. Helmholz, H. F. A Comparison of Mandelic Acid and Sulfanilamide as Urinary Antiseptics, *ibid* **109** 1039-1041 (Sept 25) 1937. Bliss, E. A., and Long, P. H. Failure of Para-Aminobenzenesulfonamide Therapy in Urinary Tract Infections Due to Group D (Lancefield) Beta Hemolytic Streptococci, *New England J Med* **217** 18-21 (July 1) 1937.

Several studies⁵⁵ suggest the effectiveness of sulfanilamide in the treatment of malaria, but Hill and Goodwin,⁵⁶ who tried it on 100 patients and obtained good results, do not recommend its use, because of its toxic effects. The drug had no therapeutic value in the treatment of mice inoculated with *Bacillus pertussis*⁵⁷ but was apparently effective in the treatment of "sniffles"⁵⁸ of rats kept in laboratory colonies. A few patients with bubonic plague recovered after receiving prontosil, a derivative of sulfanilamide (the disodium salt of 4-sulfamidophenyl-2'-azo-7'-acetyl-amino-1'-hydroxynaphthalene-3',6'-disulfonic acid)⁵⁹

Investigators⁶⁰ at the National Institute of Health found prontosil⁶¹ to have a protective action in mice against infection with the virus of lymphocytic choriomeningitis when large doses were given shortly after inoculation with small amounts of virus. The drug or its related compounds had no effect on infections caused by the viruses of St. Louis encephalitis or influenza. Others^{61a} have obtained more promising results in the treatment of experimental influenza. Dochez and Slanetz⁶² obtained results which indicated the effectiveness of sodium sulfamyl-sulfanilate ($\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_2 \cdot \text{NH} \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_3\text{Na}$) when given to ferrets inoculated with the virus of canine distemper. The drug prevented the disease promptly when administered shortly after the development of symptoms and fever. Secondary bacterial infection seemed at times to hamper the favorable action of the drug. Marcus and Necheles⁶³ report good results in treating spontaneous infection of distemper in dogs with

55 van der Wielen, Y. Prontosil in Quartan Malaria, *Nederl tijdschr v geneesk* **81** 2905-2910 (June 19) 1937. Diaz de Leon, A. Treatment of Malaria with Sulfonamide Compounds, *Pub Health Rep* **52** 1460-1462 (Oct 15) 1937.

56 Hill, R. A., and Goodwin, M. H. Prontosil in the Treatment of Malaria, *South M J* **30** 1170-1171 (Dec) 1937.

57 Gross, P., Cooper, F. B., and Lewis, M. Chemotherapy of B. Pertussis Infections of Mice, *Proc Soc Exper Biol & Med* **38** 407 (April) 1938.

58 Maer, N. R. F. The Treatment of "Sniffles" in the Rat with Sulfanilamide, *Science* **87** 439 (May 13) 1938.

59 Carman, J. A. Prontosil in the Treatment of Oriental Plague, *East African M J* **14** 362-365 (Feb) 1938.

60 Rosenthal, S. M., Wooley, J. G., and Bauer, H. Studies in Chemotherapy VI. The Chemotherapy of Choriomeningitis Virus Infection in Mice with Sulphonamide Compounds, *Pub Health Rep* **52** 1211-1217 (Sept 3) 1937.

61 The prontosil used was 4-sulfamido-2'-4'-diaminoazobenzene hydrochloride.

61a Chlmenko, D. R., Crossley, M. L., and Northey, E. H. The Protective Action of Certain Sulfanilamide Derivatives in Experimental Influenza Infections, *J A M A* **110** 2099-2100 (June 18) 1938.

62 Dochez, A. R., and Slanetz, C. A. The Treatment of Canine Distemper with a Chemotherapeutic Agent, Sodium Sulfamyl Sulfanilate, *Science* **87** 142-144 (Feb 11) 1938.

63 Marcus, P. M., and Necheles, H. Treatment of Spontaneous Canine Distemper with Sulfanilamide, *Proc Soc Exper Biol & Med* **38** 385-387 (April) 1938.

the drug, but the experience of Dickerson and Whitney⁶⁴ was disappointing in this regard. No evidence was found for the effectiveness of the drug in the disease.

The foregoing brief review clearly indicates that sulfanilamide and its related compounds are remarkable chemotherapeutic agents with unlimited possibilities for future development. But it is unwise perhaps to expect too much. One has but to recall the enthusiasm with which amsphenamine was received as a possible cure for all infections, yet in spite of years of effort, no modifications of it have been found to influence the course of any infection aside from a few which are caused by spirochetes. It is far too early to estimate the actual value of sulfanilamide in many of the infections mentioned. In most reports of experimental studies attention has been directed to the necessity of using large amounts of the drug and small doses of infective agent. Many more cases will have to be carefully studied together with controls before it will be wise to use the drug in general practice except for the few infections against which it is known to be of value. Despite the warnings which have been repeatedly given, the indiscriminate use of the drug for any febrile disease is deplorable. The toxic effects of the drug will not be considered here. Suffice it to say that cyanosis, jaundice, agranulocytosis, anemia, optic neuritis, cutaneous eruptions, fever and other unpleasant and dangerous side effects have been reported, many of them in the Sept. 25, 1937, issue of *The Journal of the American Medical Association*.

Many investigators are at present attempting to discover new compounds which have a greater toxic effect on the infecting agents and are less toxic for the host. Bauer and Rosenthal⁶⁵ report that disulfanilamide (paraaminobenzenesulfonylsulfonamide, $\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_2\text{NH} \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_2\text{NH}_2$) administered orally had a therapeutic index of 5, while that of sulfanilamide was only 3.3. Another compound, studied by Buttle, diaminodiphenylsulfone ($\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{NH}_2$), was thirty times as active against streptococci as sulfanilamide but was also highly toxic for the host. Fourneau used an acetyl derivative of diaminodiphenylsulfone ($\text{CH}_3 \cdot \text{CO} \cdot \text{HN} \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{COCH}_3$), and Bauer used a water-soluble formaldehyde sulfoxylate derivative ($\text{NaSO}_2 \cdot \text{CH}_2 \cdot \text{HN} \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{SO}_2\text{Na}$). All three of these sulfones are claimed to be superior to sulfanilamide for treatment of pneumococcic infections in mice, but, as Bauer and Rosenthal conclude, "in mice the action is still considerably less marked than against

64 Dickerson, V. C., and Whitney, L. F. Sulfanilamide and Prontosil in the Treatment of Canine Distemper, *Proc. Soc. Exper. Biol. & Med.* **38** 263-264 (March) 1938.

65 Bauer, H., and Rosenthal, S. M. Studies in Chemotherapy. VII. Some New Sulphur Compounds Active Against Bacterial Infections, *Pub. Health Rep.* **53** 40-49 (Jan. 14) 1938.

streptococci, and, while marked prolongation of life can be achieved, few animals permanently survive pneumococcal infections as a result of therapy" Other workers⁶⁶ have found 4,4'-diacetylaminodiphenyl-sulfone to be more effective than sulfanilamide in hemolytic streptococcal infection of mice. It is also less toxic for mice.

ACUTE RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

British investigators⁶⁷ present further evidence to establish an etiologic relation between certain "elementary bodies" and acute rheumatic fever. The elementary bodies are found in the serous effusions in acute rheumatic fever and in other diseases as well, but the ones found in rheumatism are more uniform in size and more abundant. They are specifically agglutinated by serum from other patients with rheumatic fever. There is also some cross agglutination with serum from patients with rheumatoid (infectious) arthritis and chorea. This, the authors believe, supports the view that an etiologic relation between rheumatic fever, chorea and rheumatoid arthritis exists, as suggested by others.

Any one interested in the treatment of acute infections, particularly of acute rheumatic fever, will profit by reading a paper by Wilson⁶⁸ on the natural history of the disease. Much unwarranted enthusiasm arising from the supposedly curative effects of various remedies applied in treatment could be avoided if one realized how easy it is to be misled by the natural remissions of any disease. According to Wilson, the natural course of rheumatic fever as observed is apparently uninfluenced by any form of treatment. Jordan's⁶⁹ observations confirm these views as far as vaccine treatment for rheumatism is concerned. Vaccine therapy for rheumatic fever and rheumatoid arthritis, he believes, and I do also, rests on empiricism, no evidence exists to justify its use as being of specific value. Vaccines may be tried as an experimental procedure in selected cases if the patients are kept under close observation, but they should not be used routinely.

In another study Wilson and Schweitzer⁷⁰ endeavored to show the existence of a hereditary factor in the susceptibility to rheumatic fever.

66 Cooper, F. B., Gross, P., and Lewis, M. Sulfone and Sulfanilamide Therapy in Streptococcal Infections, *Proc Soc Exper Biol & Med* **38** 375-377 (April) 1938.

67 Eagles, G. H., Evans, P. R., Fisher, A. G. T., and Keith, J. D. Virus Etiology of Rheumatic Disease, *Lancet* **2** 421-428 (Aug 21) 1937.

68 Wilson, M. G. The Natural History of Rheumatic Fever in the First Three Decades, *J Pediatr* **10** 456-465 (April) 1937.

69 Jordan, E. P. Critical Evaluation of Vaccine Therapy in Rheumatism, *J A M A* **109** 1444-1445 (Oct 30) 1937.

70 Wilson, M. G., and Schweitzer, M. D. Rheumatic Fever as a Familial Disease. Environment, Communicability and Heredity in Their Relation to Observed Familial Incidence of Disease, *J Clin Investigation* **16** 551-570 (July) 1937.

There appears to be a familial tendency for the disease to develop, but other factors, such as environment and exposure, no doubt are also essential for infection to take place. The authors conclude that susceptibility to rheumatic fever is transmitted as a single autosomal recessive gene. They observed that the resulting rheumatic activity had no direct relation to the type and the source of exposure. Rheumatic fever followed either active or inactive exposure. Intimate contact with a source of infection in a patient with active rheumatic fever, called familial exposure, was of no greater significance than casual contact or extrafamilial exposure in inciting the disease.

In a dietary study⁷¹ of rheumatic fever, children with the disease were given a special diet of high caloric value and were compared with other children with rheumatic fever who received ordinary hospital food. There was a significant gain of weight in those who partook of the special diet, but no other beneficial effects were noted. Since gain in weight and good nutrition are usually desired in rheumatic fever, the special diet is recommended.

Bland and Jones⁷² studied 306 fatal cases which occurred among 1,500 persons under the age of 21 with rheumatic fever. Rheumatic fever was the chief cause of death in 250 cases (82 per cent). The clinical manifestations in fatal cases of the disease differed somewhat from the typical picture, arthritis, for example, was not present in any case in the course of the terminal illness, abdominal and precordial pain were more troublesome. Chorea was rarely seen in these cases, subcutaneous nodules were present in 60 per cent but carditis was present in every case. Pericarditis was noted in about 35 per cent clinically and in 80 per cent post mortem. Evidence of pulmonary and hepatic involvement was common.

In further studies on the subject Gouley⁷³ points out the frequency with which pneumonitis occurs in patients with rheumatic fever, particularly with severe infection. The pulmonary inflammation in the earliest stages is not caused by secondary invading bacteria but is an integral part of the disease. The clinical manifestations are often overshadowed by other symptoms or overlooked if examination of the lungs is omitted. There is often marked disproportion between the mild symptoms referable to a pneumonic infiltration and the extent of the

71 Sadow, S. E., Hubbard, J. P., and Jones, T. D. A Dietary Study in Rheumatic Fever, *New England J. Med.* **217** 170-174 (July 29) 1937.

72 Bland, E. F., and Jones, T. D. Fatal Rheumatic Fever, *Arch. Int. Med.* **61** 161-171 (Feb.) 1938.

73 Gouley, B. A. The Acute and Subacute Pulmonary Involvement in Rheumatic Fever with Notes on the Complication of Basal Pulmonary Collapse, *Ann. Int. Med.* **11** 626-636 (Oct.) 1937.

lesion as shown by a roentgenogram. Respiratory distress is usually slight unless the consolidation is massive. The acute lesion may result in inflammatory collapse and subsequent fibrosis. The problem was also studied by Melnick ^{73a}

Only a few of the papers dealing with rheumatic diseases are mentioned here. For a comprehensive review of the subject the reader is referred to the "Fourth Rheumatism Review" of Hench and his associates ⁷⁴. This review of publications concerning one group of diseases alone, rheumatism, extracts information from over six hundred papers and books published in the English language in a single year and occupies 156 pages.

FOCAL INFECTION

Ash's ⁷⁵ recent paper adds more data to the accumulating evidence with which the overenthusiasm in the concept of focal infection can be combated. She refers to Kaiser's valuable studies, which have done so much to check the indiscriminate removal of tonsils, and feels that even his conclusions are somewhat too optimistic in regard to the beneficial effects of tonsillectomy in rheumatic fever. Ash feels that it is debatable whether tonsils serve as the portal of entry or a focus of infection for the etiologic agent of rheumatic fever. Rheumatic fever occurs in persons whose tonsils have been removed and also in those in whom acute or chronic infection of the tonsils is absent. In the series of cases reported Ash found that tonsillectomy had no influence on the incidence of recurrent attacks, there was also no significant difference between the death rate for the children whose tonsils had been removed before the onset of the disease and that for the children whose tonsils were removed subsequently or had never been removed. Rheumatic exacerbations followed in a high proportion of cases in which the tonsils were extirpated early in the course of the disease. Similar findings had previously been reported by Wilson, Lingg and Croxford, Campbell and Warner, and Wallace and Smith. These conclusions can be reconciled with Kaiser's statistics, which showed that the mortality rate appeared to be much less for tonsillectomized children, by regrouping the statistics and analyzing them differently.

^{73a} Melnick, P. J. Pulmonary Changes in Rheumatic Fever, *Illinois M. J.* **73**:336-339 (April) 1938.

⁷⁴ Hench, P. S., Bauer, W., Ghrist, D., Hall, F., Holbrook, W. P., Key, J. A., and Slocumb, C. H. The Present Status of Rheumatism and Arthritis. Review of American and English Literature for 1936 (Fourth Rheumatism Review), *Ann. Int. Med.* **11**: 1089-1247 (Jan.) 1938.

⁷⁵ Ash, R. Influence of Tonsillectomy on Rheumatic Infections, *Am. J. Dis. Child.* **55**: 63-75 (Jan.) 1938.

No reconciliation is possible, however, with the unwarranted conclusions drawn by Turnley⁷⁶ This author advises removal of tonsils in all cases of rheumatism, among which are included instances of "painful conditions of the muscles, fascia, bones, nerves and joints" His listing of conditions which he says are indications for tonsillectomy is more dangerous than ludicrous, for he mentions cheesy plugs in the tonsil, keratosis due to *Leptothrix*, conjunctivitis, optic neuritis, run-down conditions, harboring of diphtheria bacilli, cardionephritis, certain thyroid disorders and asthma Worst of all, tonsillectomy is recommended as a prophylactic measure against tuberculosis and Hodgkin's disease In a previous publication this author made the preposterous suggestion that there would be a healthier and better race if children had their tonsils and adenoids removed before the age of 5 or 6 years

To complicate an obscure problem still further, Gehlen⁷⁷ regards polyarthritis as a spinal dystrophic articular disease resulting from the effects of a "toxin" elaborated in foci of infection How the author arrives at his conclusions is a mystery, for no proof or bacteriologic studies of the existence of a toxin are presented Gutzeit⁷⁸ states that diseased or infected teeth can be recognized by subjecting them to short wave irradiation with a specially adapted apparatus When healthy teeth are irradiated, an acceleration of the sedimentation rate of the erythrocytes is not caused, but if "diseased" teeth are so treated the "toxic" substances present enter the circulation and disturb the suspension stability of the blood He admits that the extraction of teeth giving a positive reaction did not always cause improvement in general symptoms

Such papers as those of Turnley, Gehlen and Gutzeit are cited merely as examples to warn clinicians to scrutinize thoroughly all evidence before applying dangerous methods of treatment of any kind to their patients Editors of medical journals could prevent the dissemination of much misinformation by demanding the inclusion of rigid control tests and by more liberal use of a blue pencil on unsupported expressions of opinion

Cecil, once an advocate of the removal of foci of infection in the treatment of rheumatoid arthritis, has changed his mind on the subject

76 Turnley, W H Tonsillectomy for Rheumatism A Study of 3,172 Cases, *Ann Otol, Rhin & Laryng* **46** 1050-1059 (Dec) 1937, The Results of 76,000 Adenoid and Tonsil Operations, *Laryngoscope* **47** 1-6 (Jan) 1937

77 Gehlen, H Neuere Erkenntnisse auf dem Krankheitsgebiet der primär chronischen Polyarthritis und ihre Auswertung für die Therapie, *Verhandl d deutsch Gesellsch f inn Med* **49** 377-383, 1937

78 Gutzeit, K Zur Frage der dentalen Infektion und ihrer Diagnosestellung durch Kurzwellenprovokation der Zähne, *München med Wchnschr* **85** 164-166 (Feb 4) 1938

In an address before the American College of Physicians last spring, he and Angevine gave the results of their follow-up study of patients with arthritis who had had various supposed foci of infection removed. In no instance was the course of the disease arrested, nor was the patient cured by tonsillectomy. Almost no benefit was obtained from the extraction of teeth or operations on the sinuses. They believe that the time has come for a revaluation of the theory of focal infection.

A study made in thirty-one schools in England^{78a} led a committee to conclude: "Though realizing the value of operations in carefully selected cases, we have grave doubts as to whether the majority of tonsillectomies performed today are the result of true discrimination rather than of routine ritual." Similar views are expressed by Glover and others^{78b}. In the United States tonsillectomy comprises one third of all surgical operations. Tonsillectomy was performed on at least three times as many persons who were well-to-do as on poorer ones. One can scarcely avoid the conviction that something must be gravely wrong in this practice and that it is time to call attention to the needlessness in most cases of removing the tonsils or teeth in the hope of preventing or influencing systemic diseases. I have attacked the concept of focal infections pertaining to teeth and tonsils in each of my three previous annual reviews in the ARCHIVES.

COCCIC DISEASES

Staphylococcal Infections—Accumulating evidence is providing a more optimistic outlook for the treatment of staphylococcal infections. In reviews of the subject both Rigdon⁷⁹ and Bigger⁸⁰ write favorably of the therapeutic effects of staphylococcus antitoxins. According to Rigdon, vaccines have little therapeutic effect, but toxoid seems to be of value in certain cases of chronic infection. Antitoxin likewise appears to be of value in the treatment of certain acute staphylococcal infections accompanied by toxemia. Bigger strongly advises against surgical intervention during a staphylococcal infection except when liquefaction has occurred. Incision even then should never transgress the protective zone. He also favors the use of antitoxin and toxoid. Downie,⁸¹ in

78a Epidemics in Schools, Medical Research Council, Special Report Series, no 227, London, His Majesty's Stationery Office, 1938.

78b A Criticism of Tonsillectomy, Foreign Letters, J A M A **111** 181 (July 9) 1938.

79 Rigdon, R H. Staphylococcal Immunity. Resume of Experimental and Clinical Studies, Arch Path **24** 233-245 (Aug.) 1937.

80 Bigger, J W. The Staphylococci Pathogenic for Man, Brit M J **2** 837-841 (Oct 30) 1937.

81 Downie, A W. A Comparison of the Value of Heat-Killed Vaccines and Toxoid as Immunizing Agents Against Experimental Staphylococcal Infection in the Rabbit, J Path & Bact **44** 573-587 (May) 1937.

experimental studies, was unable to increase the resistance of rabbits to staphylococcic infections of the skin by vaccinating them with staphylococcus vaccines

Neter⁸² found that staphylococci from human sources may produce either fibrinolysin or anticoagulant, or they may possess both or neither of these properties. Staphylococci pathogenic for man may produce either fibrinolysin or anticoagulant. In patients infected with a staphylococcus able to cause fibrinolysis, a specific antifibrinolysin may develop. The fibrinolysin, unlike the one of the hemolytic streptococcus, dissolves clots of both human and animal blood. The anticoagulant likewise inhibits coagulation of human and of animal plasma. It can be neutralized by normal serum, and it is not antigenic. The plasma-clotting factor is sometimes present in exudates. It may be inhibited by the anticoagulant of staphylococci or of other bacteria without being destroyed.

Gonorrhea—Vonderlehr and Usilton⁸³ made some important studies on the incidence of gonorrhea. At least a million new cases occur in the United States annually, and nearly half a million persons with the disease are under treatment, thus gonorrhea seems to be more prevalent than any other serious infectious disease. The incidence of the infection is greatest in small cities, and the mean age of persons acquiring the infection is about 24 years. There is no evidence that the incidence of gonorrhea is declining. Carpenter⁸⁴ made a comparative study of various methods for the diagnosis of gonorrhea. The culture method is the most reliable. The use of stained smears, although much simpler, may give rise to error, since other gram-negative cocci may be mistaken for gonococci. The complement fixation test as generally performed is not satisfactory or reliable. Warren and his associates⁸⁵ continue to report good results from fever therapy in gonorrheal infections. At the meeting of the Association of American Physicians in May, Bauer reported favorable results in the treatment of gonorrheal arthritis with sulfanilamide.

82 Neter, E. Fibrinolytic, Anticoagulating and Plasma-Clotting Properties of Staphylococci, *J. Bact.* **34** 243-253 (Sept.) 1937.

83 Vonderlehr, R. A., and Usilton, L. J. The Gonorrhea Problem in the United States, *J. A. M. A.* **109** 1425-1427 (Oct. 30) 1937.

84 Carpenter, C. M. The Diagnosis of Gonococci Infection in the Male. An Evaluation of Laboratory Methods, *J. A. M. A.* **109** 1328-1430 (Oct. 30) 1937.

85 Warren, S. L., Scott, W. W., and Carpenter, C. M. Artificially Induced Fever for the Treatment of Gonococcic Infection in the Male, *J. A. M. A.* **109** 1430-1434 (Oct. 30) 1937.

The problem of latency of gonococcic infection was investigated by Spink and Keefer⁸⁶ Peisons may harbor gonococci in the body for years without symptoms to indicate their presence, yet when some unrelated circumstance, such as a cold or pregnancy occurs, the bacteria become active and cause disease. Gonorrheal arthritis may develop in a person who gives no history of previous urethritis.

Meningococcic Meningitis—In classifying the types of meningococci obtained from patients with meningococcic infection since 1930, Branham and Carlin⁸⁷ found that among 409 strains, 86 per cent were of group I-III and only 11.7 per cent of type II. Among 42 strains isolated from healthy carriers, 57 per cent were of type II and 28 per cent of group I-III. Most of the persons from whom group I-III meningococci were recovered were in immediate contact with patients suffering from infection caused by the same types of meningococci. Type II meningococci were apparently relatively unimportant as a cause of disease in the period when the study was made.

In another study Branham and her associates⁸⁸ succeeded in causing purulent meningitis in guinea pigs by the intracisternal injection of living or heat-killed meningococci without the aid of mucin to enhance the virulence of the bacteria. Filtrates of broth cultures containing hypothetic toxins also caused the production of purulent exudate. Meningitis may therefore be caused both by infection and by intoxication. Antimeningococcus serum had no effect in protecting animals from meningitis.

A group of United States Army medical officers⁸⁹ took the opportunity of testing the value of intradermal reactions to discover persons liable to meningococcic infection and to study the effect of prophylactic immunization among members of the Civilian Conservation Corps. Fifty-three per cent of 7,339 subjects tested showed a 1 plus or greater reaction to the intradermal injection of meningococcus "toxin" or filtrate from broth cultures of meningococci. Those who reacted positively and were presumably susceptible to infection were given several injections of filtrate and were retested two months later. At this time 80

86 Spink, W. W., and Keefer, C. S. Latent Gonorrhea as a Cause of Acute Polyarticular Arthritis, *J. A. M. A.* **109** 325-328 (July 31) 1937.

87 Branham, S. E., and Carlin, S. A. A Study of Meningococci Recovered in the United States Since 1930, *J. Bact.* **34** 275-283 (Sept.) 1937.

88 Branham, S. E., Lillic, R. D., and Pabst, A. M. Experimental Meningitis in Guinea Pigs, *Pub. Health Rep.* **52** 1135-1142 (Aug. 20) 1937. Branham, S. E., and Pabst, A. M. Serum Studies in Experimental Meningitis, *ibid.* **52** 1143-1150 (Aug. 20) 1937.

89 Kuhns, D. M., Kisner, P., Williams, M. P., and Moorman, P. L. The Control of Meningococcic Meningitis Epidemics, *J. A. M. A.* **110** 484-487 (Feb. 12) 1938.

per cent showed a negative or nearly negative reaction. They report twenty outbreaks of meningitis in which it appeared that immunization with filtrates seemed to limit or prevent the spread of infection.

BACILLARY DISEASES

Tuberculosis—Amberson⁹⁰ points out the importance of recognizing the early lesion of pulmonary tuberculosis, which, in general, the members of the medical profession seem rather slow to comprehend. Most often in early life the first effect of infection with tubercle bacilli is the development of a small patch of pneumonitis usually in the upper portion of one lung. The symptoms arising from the lesion are usually so mild as to be unrecognized or to be regarded as the result of an unimportant infection of the respiratory tract. Abnormal physical signs are usually absent. As a matter of fact, in most cases the pneumonic area is discovered accidentally in periodic routine health examinations or when roentgenograms of the chest are made after a tuberculin test is found to show a positive reaction. The early lesion may heal completely or may leave calcified remnants, but in unfavorable cases the area may caseate, spread and result in cavitation. The infection may remain dormant for many years before spreading. Similar views are expressed by Hetherington.⁹¹ Myers does not approve of sending a patient with the first infection type of mild tuberculous pneumonia to a sanatorium. The patient should, he believes, be treated at home and should be kept in bed only until evidence of the lesion and the symptoms have disappeared.

Zavod⁹² reviews several cases of hematogenous pulmonary tuberculosis probably caused by dissemination of tubercle bacilli by way of the pulmonary artery, which, in contradistinction to generalized miliary tuberculosis, is confined chiefly to the lungs. The prognosis is favorable in most cases.

Opie and Freund⁹³ tested the relative effects of the injection of BCG and heat-killed tubercle bacilli in producing immunity to infection with tubercle bacilli. Heat-killed bacilli gave rise to immunity only slightly less in effectiveness than that produced by BCG. The injection of BCG frequently caused suppuration and abscess formation which healed spontaneously. Cutaneous sensitivity to tuberculin disappeared

90 Amberson, J. B. The Lasting Cure of Early Pulmonary Tuberculosis, *J. A. M. A.* **109** 1949-1952 (Dec 11) 1937

91 Hetherington, H. W. The Diagnosis and Management of Latent, Suspected and Early Clinical Tuberculosis, *J. A. M. A.* **109** 1952-1955 (Dec 11) 1937

92 Zavod, W. A. Hematogenous Pulmonary Tuberculosis, *J. A. M. A.* **109** 1693-1698 (Nov 20) 1937

93 Opie, E. L., and Freund, G. An Experimental Study of Protective Inoculation with Heat Killed Tubercle Bacilli, *J. Exper. Med.* **66** 761-788 (Dec) 1937

one or two years after injection of heat-killed bacilli. Other observers⁹⁴ injected BCG intradermally in children and produced cutaneous sensitivity in 80 per cent. Subcutaneous injection caused cutaneous sensitivity in 60 per cent of the cases. Sensitivity reached its maximum in six months and diminished rapidly, so that most children no longer gave positive reactions to tuberculin after two years.

Russian investigators⁹⁵ infected rabbits with tubercle bacilli and subsequently inoculated them with pneumococci. The tuberculous rabbits were able to cope with pneumococci inoculated intravenously or intraperitoneally as well as healthy control rabbits, but in the former the reaction took a slower course, had a more exudative character and tended more to necrosis.

Aronson and Meranze⁹⁶ studied the effect of syphilis on experimentally produced tuberculous lesions in rabbits. In syphilitic rabbits the local inflammatory reaction after the injection of tubercle bacilli into the skin was more prompt and intense than after similar injections in normal rabbits. Histologically the lesions in the syphilitic animals resembled the lesions characteristic of an initial syphilitic infection, suggesting that the cells of the rabbit are so modified by the disease that the introduction of an unrelated bacterium elicits an inflammatory reaction characteristic of the initial syphilitic lesion. Later, the appearance of epithelioid cells and caseation resembled the usual reaction to tubercle bacilli.

In a scholarly paper Long⁹⁷ discusses the great variability of diseases caused by different varieties of mycobacteria, including tuberculosis, leprosy, "skin-lesion" disease of cattle, Johne's disease and rat "leprosy." These diseases are generally characterized by the presence of bacilli which are regarded as acid fast because of the presence of certain related chemical substances. The tissue responses to infection are similar in these diseases, there are extensive proliferation and accumulations of monocytes, which develop into "epithelioid" cells.

In a critical review Miller^{97a} discusses a number of unsolved problems relating to tuberculosis which deserve thoughtful consideration.

94 Kereszturi, C., Rosenberg, H. A., and Park, W. H. Tuberculin Allergy Produced by Parenteral BCG Vaccination, *Am Rev Tuberc* **36** 90-99 (July) 1937.

95 Weissfeiler, J., Morozova, E. N., and Strukov, G. I. The Course of Experimental Pneumococcus Infection in Tuberculous Rabbits, *Am Rev Tuberc* **37** 93-99 (Jan.) 1938.

96 Aronson, J. D., and Meranze, D. R. The Effect of Syphilis on Local Tuberculous Lesions in Rabbits, *Am J Path* **14** 163-175 (March) 1938.

97 Long, E. R. Tuberculosis, Leprosy and Allied Mycobacterial Diseases, *Science* **87** 23-31 (Jan. 14) 1938.

97a Miller, J. A. Some Unsolved Problems of Tuberculosis, *J A M A* **111** 111-117 (July 9) 1938.

Undulant Fever—An excellent description⁹⁸ of the pathologic anatomy of undulant fever has been published in Germany. Drei⁹⁹ calls attention to hepatomegaly as a sequela of undulant fever. Another investigator¹⁰⁰ in Italy showed that flies can be experimentally infected with *Brucella* and may serve as carriers for over a week. Deem¹⁰¹ recovered *Brucella abortus* from 9 of 15 horses with fistulous withers or poll evil. The blood of 82 per cent of 34 horses with the disease agglutinated *Brucella*. Of 100 normal horses, 97 per cent gave positive reactions for *Brucella* in low dilution.

In a clinical study Beatty¹⁰² points out the frequency with which pulmonary symptoms occur in undulant fever. Many patients, particularly those with the chronic type of infection, present themselves with symptoms of pulmonary involvement. They may complain of burning sensations or pain in the chest, malaise and cough without sputum or with mucoid, mucopurulent sputum. Hemoptysis is occasionally noted. The symptoms are likely to lead to an erroneous diagnosis of pulmonary tuberculosis. Among 47 patients with undulant fever, 31 had symptoms of involvement of the respiratory tract, 18 had cough, 18 raised sputum, 5 had hemoptysis and 26 complained of pain in the chest. In several cases of acute involvement, small patches of dulness, with rales and bronchial breathing, were found. Roentgenograms showed infiltration near the hilus and an increase in density in the peribronchial areas.

Hardy, Frant and Kroll¹⁰³ point out how variable the incubation period of undulant fever is. Infection with the more virulent *melitensis* variety is followed by a comparatively short period of incubation, while in naturally infected persons small doses of the *abortus* variety may result in a prolonged period. Their study was made on 17 residents of New York who drank pasteurized milk during residence in the city but who were known to have drunk raw milk during a visit elsewhere. The incubation period of the disease in these patients was found to vary from one week to four months, with the average time much more

98 von Albertini, A., and Lieberherr, W. Beiträge zur pathologischen Anatomie der Febris undulans Bang, Frankfurt Ztschr f Path **51** 69-97, 1937

99 Drei, G. Considerazioni cliniche sul reperto frequente di esatomegalia come postumo di febbre ondulante, Gior di clin med **18** 1368-1377 (Oct 30) 1937

100 Negro, G. Significato della mosca domestica nella diffusione della febbre ondulante, Gior di batteriol e immunol **19** 17-29 (July) 1937

101 Deem, A. W. *Brucella Abortus* in Horses, J Infect Dis **61** 21-25 (July-Aug) 1937

102 Beatty, O. A. Manifestations of Undulant Fever in the Respiratory Tract, Am Rev Tuberc **36** 283-289 (Aug) 1937

103 Hardy, A. V., Frant, S., and Kroll, M. M. The Incubation Period in Undulant Fever, Pub Health Rep **53** 796-803 (May 20) 1938

prolonged than that of *Br melitensis* infection as noted in Malta and tested experimentally in Puerto Rico

Tularemia—Two papers have been published which reemphasize the frequency with which tularemia affects the lungs¹⁰⁴ In several patients, pulmonary symptoms were predominant and ushered in the disease Three patients were shepherders who were bitten by ticks prior to the onset of the disease, but it is uncertain as to whether the bacilli were inoculated in this manner or otherwise All 4 patients recovered, 3 were treated symptomatically, and 1 was given antitularensis serum

The frequency with which pneumonia is found in cases of tularemia brings out further resemblances between this disease and plague Tularemia, like plague, occurs in three clinical forms bubonic, pneumonic and septicemic or typhoid, the causative bacteria are closely related, similar animal species serve as reservoirs of infection and both diseases may be conveyed to man by direct contact with infected flesh or blood, by inhalation and by insects A similar relation may pertain to the disease called pseudotuberculosis, as I pointed out several years ago¹⁰⁵

Foshay¹⁰⁶ claims that septicemia is the chief cause of death in cases of tularemia, the mortality rate of patients with tularemic pneumonia is about 30 per cent It is true, of course, that the mortality rate is higher in most diseases when the blood stream is invaded, but whether the septicemia per se is chiefly responsible is not so certain In persons severely ill with infection, bacteria, as a result, are able to survive in the blood stream Foshay continues to report good results following the use of his antitularensis serum in the treatment of tularemia, but the product was not accepted by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in New and Non-official Remedies, the publication of other corroborative data being awaited

An excellent review of the pathology of tularemia has been published by Lillie and his associates¹⁰⁷

104 Winter, M D, Farrand, B C, and Herman, H J Tularemia, Pulmonic Form Report of Four Recoveries, *J A M A* **109** 258-262 (July 24) 1937 Blackford, S D, and Archer, V W Roentgen Study of a Nonfatal Case of Bilateral Tularemic Pneumonia Treated with Specific Serum, *ibid* **109** 264-265 (July 24) 1937

105 Reimann, H A, and Rose, W B The Similarity of Pseudotuberculosis and Tularemia, *Arch Path* **11** 584-588 (April) 1931

106 Foshay, L Cause of Death in Tularemia, *Arch Int Med* **60** 22-38 (July) 1937

107 Lillie, R D, Francis, E, and Parker, R R The Pathology of Tularemia, National Institute of Health Bulletin 167, United States Treasury Department, Public Health Service, 1937, pp 1-217

Tularemia has only recently been identified in Germany¹⁰⁸ Characteristically it was thought to be a "new" disease, never having been reported before Unnecessary alarm was immediately raised, and importation of wild rabbits from Czechoslovakia and Austria was prohibited Tularemia was recognized for the first time in Czechoslovakia and Austria a year or two ago, but, as has been demonstrated in other countries, the disease has perhaps been enzootic in rodents as long as rodents have existed in the region Cases in human beings in the past no doubt have been mistaken for cases of other diseases Ticks from rabbits in Alaska have been found to be infected with *Pasteurella tularensis*^{108a}

Three patients with obscure illness resembling tularemia were studied in England¹⁰⁹ All 3 had hunted rabbits in Ireland, and at about the same time an epizootic of undetermined origin among cats was reported In 1 case operation was performed, and the liver was found to contain lesions like those observed in tularemia, yet agglutinins for *Pasteurella tularensis* were absent Each patient had eosinophilia The authors suggest that diseases resembling tularemia and caused by closely related bacteria exist Their suggestion brings to mind the possibility of the occurrence of a disease in man caused by *Pasteurella pseudotuberculosis*, a bacterium occasionally found in diseases of animals Three French authors¹¹⁰ report a case of pseudotuberculosis which resembled typhoid with icterus A rat infected with *P. pseudotuberculosis* was trapped in Washington, D C^{110a} The lesions produced by inoculating the bacilli into other animals resembled those of plague

Plague—Studies by Eskey¹¹¹ show that not all varieties of fleas are important in the transmission of plague Female fleas seemed to be more dangerous as transmitters than males In warmer localities where *Xenopsylla cheopis* is the only type of rat flea found, epizootics flare up and die out quickly, for the flea soon succumbs to infections The flea readily transmits plague to man In cold climates the Cera-

108 Tularemia in Germany, Foreign Letters, J A M A **110** 1502-1503 (April 30) 1938

108a Philip, C B, and Parker, R R Occurrence of Tularemia in the Rabbit Tick (*Haemaphysalis Leporis-Palustris*) in Alaska, Pub Health Rep **53** 574-575 (April 15) 1938

109 Thomson, A P, Wilson, G H, and McDonald, S Three Cases of Unusual Illness with Eosinophilia, One with Lesions in the Liver Resembling Those of Tularemia, Lancet **2** 9-11 (July 3) 1937

110 Dujardin-Beaumetz, E, Ballet, B, and Cebron, J Pseudo-tuberculose chez l'homme, Presse med **46** 43-44 (Jan 8) 1938

110a Haas, V H A Study of Pseudotuberculosis Rodentium Recovered from a Rat, Pub Health Rep **53** 1033-1038 (June 24) 1938

111 Eskey, C R Recent Development in Our Knowledge of Plague Transmission, Pub Health Rep **53** 49-57 (Jan 14) 1938

tophyllus fasciatus variety is much less dangerous to man. The unusually low incidence of plague in human beings transmitted from wild rodents in the western part of the United States (sylvatic plague) is believed to be due to the fact that the fleas of these animals do not attack man. Only 40 cases in human beings have been recorded, and in many of these cases infection was probably acquired by direct contact with infected tissue or blood without the agency of fleas, and in others evidence shows that infection may have occurred from bites of domestic rat fleas (murine plague). The transmission of plague to man therefore seems to depend largely on the species of flea involved. Meyer¹¹² in California reports several cases of plague in human beings contracted in much the same way as is tularemia, that is, apparently directly from a sick cat and a rabbit, from a dead chipmunk and by the bite of a squirrel. All 4 patients recovered.

Meyer and his associates¹¹³ report an interesting case of chronic relapsing latent meningeal plague in a boy of 10 in whom a bubonic form of plague developed in June 1934. The child recovered to some extent but became severely ill again in July with meningeal symptoms. Improvement again occurred, until a fatal relapse followed in October. Necropsy revealed meningitis caused by *Pasteurella pestis*. Meyer reviews the literature and finds numerous examples of plague meningitis and of cases in which plague bacilli were recovered from patients many months after their original illness. He remarks that for twenty years many persons have studied the form of plague (sylvatic) which occurs in California, yet none has contracted the disease. It is apparently a different and less contagious form than murine or rat-borne plague. Meyer's study further emphasizes the clinical similarities between plague and tularemia.

Typhoid—Topley¹¹⁴ reviews the facts pertaining to the effectiveness of antityphoid vaccination and points out several important features: (a) Antityphoid vaccination, though it reduces the risk from occasional contact infection, may be much less effective when vaccinated persons are submitted to severe or continuous infection. (b) Endemic or epidemic typhoid cannot be controlled by prophylactic vaccination alone. (c) Typhoid when it occurs in persons previously vaccinated may be as severe as that in unprotected persons, and the blood stream is often invaded. (d) Antityphoid vaccination properly conducted reduces the

112 Meyer, K. F. The Sylvatic Plague Committee, *Am J Pub Health* **27** 777-785 (Aug) 1937.

113 Meyer, K. F., Connor, C. L., Smyth, F. S., and Eddie, B. Chronic Relapsing Latent Meningeal Plague, *Arch Int Med* **59** 967-980 (June) 1937.

114 Topley, W. W. C. The Role of Active or Passive Immunization in the Control of Enteric Infection, *Lancet* **1** 181-186 (Jan 22) 1938.

morbidity rate in general from four to six times (e) There is an impression that persons with latent typhoid infection or during the incubation period of the disease should not be vaccinated lest "provocative typhoid" result Provocative typhoid is presumably associated with a sudden onset a severe course and a mortality rate much higher (44 per cent) than that for the usual forms (No instructions are given how to determine whether or not a person is about to become ill with typhoid) (f) Vaccination with typhoid vaccine is a preventive measure of major importance when persons living in an uninfected area with well developed sanitary services migrate to a place where enteric infection is endemic (g) Adequate bacteriologic control of water, milk and food and control of carriers throughout the country would, with no inconvenience to the general public, reduce the incidence of enteric fever to a point at which a discussion of the role of antityphoid vaccination would become of academic interest, at least to those who stay at home

Tetanus—Abel's associates performed further experiments to illustrate the dual action of tetanus toxin In previous studies two distinct and separate actions of tetanus toxin were shown One is represented by the response of the central motor neurons which is manifested by the hyperactive reflex symptoms, and the other is represented by the direct peripheral action of the toxin on the voluntary muscles or their motor end plates The latter effect is responsible for the long-continued rigidity of the muscles and is clearly evident in a condition which has long been called local tetanus Under these circumstances there may be rigidity and contracture of one or more extremities without any signs of tactile reflex motor tetanus These effects never cause death directly unless muscles of vital function are involved, such as those of the pharynx, larynx or diaphragm

Firor and Jonas¹¹⁵ injected minute amounts of tetanus toxin directly into the anterior horns of the spinal cord The only observable symptoms resulting therefrom were reflex hyperexcitability and reflex jerks or spasms brought about by the slightest tactile stimulus In the quiet intervals between the reflex attacks the muscles were relaxed and flaccid The cause of muscle rigidity is therefore to be sought not in the action of the toxin on special centers but in its action on the voluntary muscles The experiments further show the improbability of an upward passage or diffusion of tetanus toxin within the cord and favor the hypothesis of the blood-borne distribution of tetanus toxin

The results of Abel's work in the past few years have revealed the futility of the use of massive doses of tetanus antitoxin in the treatment of tetanus Yet his papers have been apparently overlooked by many

¹¹⁵ Firor, W. M., and Jonas, A. F. Researches on Tetanus. IV. The Production of Reflex Motor Tetanus by Intraspinal Injection of Tetanus Toxin, Bull. Johns Hopkins Hosp. 62: 91-109 (Feb.) 1938

One has but to read the report of a case by Cables¹¹⁶ to realize the extent to which uncontrolled enthusiasm can influence therapy. In this case, a man with obviously mild tetanus was given 3,460,000 units of tetanus antitoxin over a period of forty-one days, the last dose was injected two days before the patient walked home. The cost of the antitoxin used, according to current prices, may be estimated at \$1,600. The therapeutic procedure used in this case might be regarded more as a test of endurance or capacity than as having any clinical or scientific value.

Gilles¹¹⁷ made a systemic investigation of the presence of tetanus bacilli or spores in the dust of the streets of a large city. He found *Clostridium tetani* to be widely distributed in street dust in spite of the minimal amounts of horse manure present in modern times. The results of his study justify the use of prophylaxis against tetanus in all cases of street accidents accompanied by lacerations or abrasions of the skin.

Tetanus toxoid. A year after the injection of three doses of alum toxoid¹¹⁸ the antitoxic titer of the blood dropped considerably but remained fairly constant when three doses (0.5, 1 and 1 cc.) of the untreated toxoid were injected. A subsequent dose of either preparation given one year after the initial injections increased the antitoxic titer of the blood from twenty to fifty times. This level of protection is higher and more persistent than that resulting from the usual prophylactic effect of the usual form of tetanus antitoxin.

Leprosy.—Two members of the United States Public Health Service dispel a certain amount of confidence which has gradually accumulated concerning knowledge of leprosy. At the International Leprosy Conference in Cairo, Egypt, Hasseltine stated that there is no specific remedy for the disease. Apparently he and many others have but little faith in the power of chaulmoogra oil or its derivatives to influence leprosy. Wade and others, however, still regard it as a valuable drug. Hasseltine outlined a plan for the establishment of a national preventorium to which children of leprous parents may be admitted immediately after birth, cared for and educated at government expense. Although the mode of infection of leprosy is unknown, there is reason to believe that the disease, like tuberculosis, is acquired not by inheritance but by long exposure to a source of infection.

116 Cables, H. A. The Amount of Antitoxin Used in a Case of Tetanus, *J. A. M. A.* **110** 1271-1272 (April 16) 1938.

117 Gilles, E. C. The Isolation of Tetanus Bacilli from Street Dust. Its Bearing on Surgical Practice, *J. A. M. A.* **109** 484-486 (Aug. 14) 1937.

118 Jones, F. G., and Moss, J. M. Studies on Tetanus Toxoid. Response of Human Subjects to an Injection of Tetanus Toxoid or Tetanus Alum Precipitated Toxoid One Year After Immunization, *J. Immunol.* **33** 183-190 (Sept.) 1937.

McCoy¹¹⁹ reiterates that the exact mode of transmission of the disease is unknown and points pessimistically to the fact that there exists no real proof of the efficiency of segregation as a measure for public health. Segregation is justified, he believes, from the point of view of the esthetic interests of a community and from that of public charity. Segregation, he believes, should be leniently enforced, particularly in regions where leprosy has no tendency to spread. Although prolonged and intimate contact seems necessary for infection to take place, nevertheless there are many cases in which no contact with known leprosy can be discovered. With the latter type of case one can only speculate as to the occurrence of latent leprosy or possible carriers as sources of infection. No laboratory animals have yet been found to be susceptible to infection with leprosy.

VIRUS DISEASES

Acute Anterior Poliomyelitis—The question of the portal of entry of the virus of poliomyelitis has again assumed importance because of interest in the use of nasal sprays in attempted prophylaxis. A number of studies have cast doubt on the efficacy of trinitrophenol-alum sprays in preventing the disease. Numbers of "protected" persons have contracted poliomyelitis. The following statement¹²⁰ was recently endorsed by several leading authorities:

There is at present no generally accepted preventive of poliomyelitis nor any effective remedy in the acute stage, other than absolute rest. Complete rest is so important in the early days of this inflammation of the central nervous system that it is usually far better to leave the child in bed at home when the disease is first suspected than to move him any appreciable distance to a hospital.

A recent polemic between Harmon¹²¹ and Lennette¹²² brings out a number of points in favor of routes of infection other than the nasopharynx. Harmon favors the gastrointestinal route of infection, as emphasized for years by Swedish investigators and by Toomey, since (1) there is no obvious contagion in poliomyelitis of man, (2) cutting the olfactory tracts does not prevent infection when the virus is inoculated intravenously, (3) monkeys do not contract the disease by the nasopharyngeal route unless heroic methods are used, (4) nasal spraying with zinc sulfate does not prevent infection when virus is given intra-

119 McCoy, G. W. Communicability of Leprosy and Application of Control Measures, *Arch. Dermat. & Syph.* **37** 169-174 (Feb.) 1938.

120 Stimson, P. M. Statement About Infantile Paralysis, *J. A. M. A.* **110** 1620 (May 7) 1938.

121 Harmon, P. H. The Use of Chemicals as Nasal Sprays in the Prophylaxis of Poliomyelitis in Man, *J. A. M. A.* **109** 1061 (Sept. 25) 1937.

122 Lennette, E. H. The Use of Chemicals as Nasal Sprays in the Prophylaxis of Poliomyelitis in Man, *J. A. M. A.* **109** 1381-1382 (Oct. 23) 1937.

venously or by mouth, (5) symptoms in some cases are present exclusively in the gastrointestinal tract, (6) the disease can be produced experimentally in monkeys by gastrointestinal inoculation, (7) the virus may be found in the nasopharynx after intracerebral or intravenous inoculation, (8) it is often impossible to isolate the virus from the nasopharynx of patients, and it can often be recovered from the rectal washings, (9) alterations in the olfactory bulbs are not always present in patients examined post mortem

Lennette in defending the concept of the nasopharynx as a portal of entry replies that (1) the presence of virus in the stool and rectal washings may be explained by virus which has been swallowed, (2) virus may not be recoverable from the nasopharynx of patients because of its presence in subinfective dosage or simultaneous presence with a neutralizing antibody, (3) virus has been recovered from the nasopharynx of a significant percentage of patients and contact carriers, and (4) his own experiments strongly suggested that infection does not occur in test animals if the olfactory nerves are cut. Lesions occur in the olfactory bulbs of animals inoculated intravenously, but complete serial sections must often be made to detect them. Each observer is critical of the size of the inoculum used by the other, claiming that overdosage may lead to erroneous conclusions.

The performance of some decisive experiments to show whether one route or the other or both may be followed by the virus in carriers of infection has not as yet been accomplished. The controversy may perhaps be clarified in part by the observation of Trask and Paul¹²³ that a generalization as to the route of infection does not apply to all strains of the virus. With some strains, for example, it is easy to infect monkeys by intracutaneous inoculation. Cutaneous infectivity seems to decrease with the age of the strain. Howe and Ecke¹²⁴ excised the olfactory tracts of monkeys and left the olfactory bulbs. In such animals after inoculation, fever developed but no paralysis. Other monkeys from which the olfactory bulbs were removed did not have fever or paralysis. The experiments are believed to suggest that the olfactory bulbs are the seat of the virus reaction. Schultz and Raffel¹²⁵ were able to concentrate the virus of poliomyelitis by means of ultracentrifugation in a vacuum.

123 Trask, J. D., and Paul, J. R. The Skin Infectivity of Poliomyelitis Virus, *Science* **87** 44-45 (Jan 14) 1938

124 Howe, H. A., and Ecke, R. S. Experimental Poliomyelitis Without Paralysis, *Proc Soc Exper Biol & Med* **37** 125-126 (Oct) 1937

125 Schultz, E. W., and Raffel, S. Sedimentation of Poliomyelitis Virus by Means of a Vacuum Ultracentrifuge, *Proc Soc Exper Biol & Med* **37** 297-299 (Nov) 1937

In an epidemic of poliomyelitis in Texas, Gilliam and Decherd¹²⁶ noted a large proportion of patients with predominant signs of bulbo-pontile involvement. Hudson and Lennette¹²⁷ obtained samples of serums from persons in Brazil and from an island near Australia to determine whether or not a specific virus-neutralizing substance was present to indicate that poliomyelitis occurs in these tropical areas. The serum from the majority of persons tested contained neutralizing properties, showing that poliomyelitis is probably worldwide in its distribution.

Encephalitis—Investigators¹²⁸ in St. Louis isolated the virus which caused the 1937 outbreak of encephalitis and found it to be immunologically identical with the one which caused an epidemic in that city in 1933. An endemic focus no doubt exists there. Evidence¹²⁹ indicates that encephalitis of the St. Louis type was present in an epidemic in California in the summer of 1937. Fifty-five per cent of 29 samples of serum from patients with acute encephalitis or polioencephalitis neutralized the virus of the St. Louis type, and none neutralized virus of lymphocytic choriomeningitis. Other interesting studies¹³⁰ showed that the lesions produced in mice by the virus of encephalitis varies in intensity with the season. The cerebral reaction is of greatest severity in winter and of least severity in summer. Artificial raising or lowering of the temperature seemed to have the same effects. In similar experiments the intensity of the cerebral lesions of experimental typhus fever of the endemic type was also in inverse proportion to the temperature both seasonally and when artificially regulated. The clinical reaction and the duration of the disease were greater in winter than in summer, and the incubation period was longer in summer than in winter.

126 Gilliam, A. G., and Decherd, G. M. Note on the Preponderance of Cases with Bulbo-pontine Involvement in a Small Outbreak of Poliomyelitis in Austin, Texas, *Pub Health Rep* **52** 1853-1854 (Dec 17) 1937.

127 Hudson, N. P., and Lennette, E. H. Incidence of Poliocidal Services in Regions Where Poliomyelitis Epidemics Are Infrequent, *Am J Trop Med* **18** 35-40 (Jan) 1938.

128 Greutter, J., Brown, G. O., Muether, R. O., and Casey, A. E. Further Studies on the Virus of the 1937 Outbreak of Encephalitis in St. Louis, *Proc Soc Exper Biol & Med* **37** 284-285 (Nov) 1937. McCordock, H. A., Smith, M. G., and Moore, E. Isolation of St. Louis Encephalitis Virus During Inter and Epidemic Periods, *ibid* **37** 288-290 (Nov) 1937.

129 Howitt, B. F. Antiviral Substances to the Virus of Encephalitis (St. Louis Type) in Serums Collected in California, *Proc Soc Exper Biol & Med* **38** 334-336 (April) 1938.

130 Lillie, R. D., Dyer, R. E., Armstrong, C., and Pasternack, J. G. Seasonal Variation in Intensity of Brain Reaction of the St. Louis Encephalitis in Mice and of Endemic Typhus in Guinea Pigs, *Pub Health Rep* **52** 1805-1822 (Dec 10) 1937.

It is known that the virus of equine encephalomyelitis can be sedimented by ultracentrifugation. It has now been shown that the immune bodies contained in the tissues of animals which have recovered from infection can likewise be concentrated by high speed centrifugation.¹³¹

Lymphocytic Choriomeningitis—Investigators¹³² in the United States Public Health Service endeavored to determine how widely the virus of lymphocytic choriomeningitis is distributed in the United States by testing the serum of persons in different localities for the presence of specific protective bodies. Since recovery from the infection is followed by the production of demonstrable specific antibodies, it is assumed that persons whose serum is protective have actually suffered from the disease at some previous time. Protective antibodies were present in the serum from 138 (11 per cent) of the 1,248 persons tested. The serum of children rarely had protective antibodies. Positive results were obtained for serums that came from widely scattered areas of the country, and in many instances a history of meningeal symptoms could not be obtained. It is suggested that numerous cases of subclinical or undiagnosed choriomeningitis occur. Often the only symptoms present in proved cases are those easily mistaken for a cold or grip. Antibodies may persist in the blood for nearly four years after an attack.

The authors found it possible to transmit the infection to monkeys by instilling the virus into the urethra or the vagina. Virus has been found in the urine and in the seminal fluid of infected animals. These facts suggest the possibility of a venereal route as one mode of infection.

A serous form of meningitis of unknown etiology is described by Fatzer,¹³³ of Switzerland. The clinical description and laboratory findings are similar to those of lymphocytic choriomeningitis. It is regarded as a disease of young swineherds and is presumably contracted from sick pigs.

Measles—Broadhurst and her associates¹³⁴ report the demonstration of inclusion bodies in the nasal mucous membranes and in the Koplik spots when preparations are stained with nigrosine. Inclusion bodies were said to be readily found in the mononuclear cells of the

131 Beard, J. W., Finkelstein, H., Sealy, W. C., and Wyckoff, R. W. G. The Ultracentrifugal Concentration of the Immunizing Principle from Tissues Diseased with Equine Encephalomyelitis, *Science* **87** 89-90 (Jan 28) 1938.

132 Wooley, J. G., Armstrong, C., and Onstott, R. H. The Occurrence in the Sera of Man and Monkeys of Protective Antibodies Against the Virus of Lymphocytic Choriomeningitis as Determined by the Serum-Virus Protection Test in Mice, *Pub. Health Rep.* **52** 1105-1114 (Aug 13) 1937.

133 Fatzer, H. Zur Frage der Meningitis serosa und der Maladie des jeunes Porchers, *Schweiz. med. Wchnschr.* **67** 709-712 (July 31) 1937.

134 Broadhurst, J., MacLean, M. E., and Saurino, V. J. Inclusion Bodies in Measles, *J. Infect. Dis.* **61** 201-207 (Sept-Oct) 1937.

blood when smears were stained with simple stains. They were present from one day before the exanthem broke out to ten days after its appearance. Inclusion bodies composed of rounded granules and compact crescentic bodies also appeared in tissue cultures of leukocytes taken from patients with measles on the third and the seventh day of the disease.

In another study,¹³⁵ cytoplasmic inclusion bodies obtained from patients with sore throat, chronic cough and other symptoms were also reported to be grown in tissue cultures. The cells containing such inclusion bodies do not show the same changes as those in cells of blood or tissue from patients with measles.

Foot and Mouth Disease—An epizootic of foot and mouth disease broke out in Germany in 1937, as described by Wagener.¹³⁶ He also points out that there are three varieties of the virus, A, B and C, and that one type does not produce immunity against the others. Human beings may become infected, and after an incubation period of several days there is fever with a diphasic character, and primary blisters develop at the portal of entry of the virus, usually on the lips, mouth and hands. Etiologic diagnosis may be established by inoculating blister fluid into the scarified skin of the feet of guinea pigs.

Yellow Fever—Soper and Smith^{136a} found yellow fever virus grown in tissue cultures when mixed with human immune serum to be a safe and effective mixture for immunization but impractical because of the small amounts available. A high percentage of failures occurred when persons were vaccinated with hyperimmune monkey serum and tissue culture virus. In 20 to 30 per cent of persons vaccinated with certain lots of vaccine, delayed reactions characterized by jaundice occurred within two to eight months. Vaccination against yellow fever is obviously not yet on a reliable basis.

The newly recognized jungle yellow fever of South America, which was at first believed to be transmitted to man by means other than the mosquito, has been transmitted by the *Aedes aegypti* mosquito under laboratory conditions.^{136b}

135 Broadhurst, J., Cameron, G., and Saurino, V. Measles Inclusion Bodies in Blood and in Tissue Culture, *J Infect Dis* **62** 6-20 (Jan-Feb) 1938.
Broadhurst, J., Cameron, G., and Taylor, I. Tissue Cultures of Human Throat Inclusion Bodies, *ibid* **62** 21-26 (Jan-Feb) 1938.

136 Wagener, K. Die Maul- und Klauenseuche als medizinisches Problem, *Med Klin* **34** 173-175 (Feb 11) 1938.

136a Soper, F. L., and Smith, H. H. Yellow Fever Vaccination with Cultivated Virus and Immune and Hyperimmune Serum, *Am J Trop Med* **18** 111-134 (March) 1938.

136b Whitman, L., and Antunes, P. C. A. Transmission of Two Strains of Jungle Yellow Fever Virus by *Aedes Aegypti*, *Am J Trop Med* **18** 135-148 (March) 1938.

The Nature of Filtrable Virus—Rawlins and Takahashi,¹³⁷ it seems, are not wholly convinced of the manimate nature of certain viruses, at least they feel that the matter is by no means settled. Other observers have believed Stanley's crystals to be composed of elongated molecules in the liquid crystalline state. The molecules tend to come together with their long axes parallel, forming submicroscopic groups called swarms. The swarms presumably come together with their long axes parallel and are then visible. Under polarized light these liquid crystals may be indistinguishable from similar groups composed of submicroscopic crystals called tactoids. The virus of tobacco mosaic disease has some of the properties of liquid crystals and tactoids. Furthermore, the molecular weight of the tobacco mosaic virus protein lies between 10,000,000 and 17,000,000, and the weight of bacteriophage is probably over 200,000,000. The highest molecular weight of known enzymes is 82,800. Because of the wide differences in weight between the virus and the enzymes, the question is raised whether or not they are, after all, quite different. These and other puzzling facts provide opportunity for much more study of the subject.

MISCELLANEOUS DISEASES

Trichinosis—Sawitz¹³⁸ made a study of the prevalence of trichinosis in the United States according to various authors who have made special studies of the subject in postmortem examinations. The incidence of trichinella infection was 12 per cent. Statistically the incidence of trichinosis has increased considerably in recent years, but this increase, as in other infectious diseases, more likely indicates that in more cases the condition is being correctly diagnosed. The mortality rate is lower than stated in other reports, which indicates that more mild cases are being recognized.

A large outbreak of trichinosis was observed¹³⁹ in a Civilian Conservation Corps camp in Vermont in October 1937. Forty-four patients required hospital treatment, and 20 remained ambulatory. All enrollees had been present at one meal and had eaten roast loin of pork which was said to have been undercooked in the center. The incubation period varied from three to twenty days, with an average of twelve days. Biopsy was made in several cases. In 1 case 800 larvae were estimated per gram of muscle. If larvae were distributed uniformly in this patient's musculature, it was estimated that over 26,000,000 were present. The

137 Rawlins, T. E., and Takahashi, W. N. *The Nature of Viruses*, Science **87** 255-256 (March 18) 1938.

138 Sawitz, W. *Prevalence of Trichinosis in the United States*, Pub. Health Rep. **53** 365-383 (March 11) 1938.

139 Ferenbaugh, T. L., Segal, L., and Schulze, H. A. *A Trichinosis Epidemic of Sixty-Four Cases*, J. A. M. A. **110** 1434-1436 (April 30) 1938.

remaining 136 healthy members of the company were given the cutaneous and the precipitin test, 20 gave positive reactions. Seven of the 20 had no symptoms of illness, 5 had been under observation for suspected trichinosis and 8 had the indefinite symptoms of a cold, with swollen conjunctivae, painful eyeballs, muscular weakness and malaise. In this epidemic, therefore, about one third of the infected persons were ambulatory, with subclinical infection.

One wonders how many patients thought to be suffering from colds actually have a mild form of some other disease. In the epidemic just reported mild trichinosis was the cause, and as stated elsewhere in this review, choriomeningitis was apparently the cause. A few years ago a number of persons in Brazil who supposedly had colds or influenza actually had yellow fever. In many cases poliomyelitis in its early stages is thought to be a cold. Pneumonic plague in California was thought to be influenza until an investigation was made. Many other examples of error could be cited.

Malaria—Important experimental studies on malaria are under way in the laboratories of the International Health Division of the Rockefeller Foundation.¹⁴⁰ A certain degree of immunity to malaria is generally believed to exist after recovery from the disease. Serum from monkeys with chronic plasmodial infection, Coggeshall and Kumm found, was effective in reducing the intensity of the primary infection in other animals. Protective antibodies appear in the blood of monkeys during experimental infection. Coggeshall¹⁴¹ inoculated monkeys with *Plasmodium knowlesi* and *Plasmodium inui*. As an immediate response, the spleen became enlarged, at times even before parasites appeared in the peripheral blood. The more virulent *P. knowlesi* caused less enlargement of the spleen than *P. inui*.

An interesting paper by Mayne¹⁴² discusses the question of protracted incubation or latency of malarial infection. In 1 patient observed the latent period between the time of infection and the manifestation of symptoms was one year. Other observers also noted long periods of six months or more. In considering the reason for the delay of evidence of disease, several factors may be operative: the condition of the patient, the season of the year when infection occurs, the size of the dose of infection and, of course, the variety of *Plasmodium* dealt with. The long latent period in malaria also may account for the development

¹⁴⁰ Coggeshall, L. T., and Kumm, H. W. Demonstration of Passive Immunity in Experimental Monkey Malaria, *J. Exper. Med.* **66** 177-189 (Aug.) 1937.

¹⁴¹ Coggeshall, L. T. Splenomegaly in Experimental Monkey Malaria, *Am. J. Trop. Med.* **17** 605-617 (July) 1937.

¹⁴² Mayne, B. Protracted Incubation in Malarial Fever, *Pub. Health Rep.* **52** 1599-1607 (Nov. 12) 1937.

of malaria in a recipient after transfusion of blood from a donor who has latent malaria. The long period of latency of malaria recalls the speculation of Zinsser regarding the latency of typhus fever. Jews living in eastern Europe, it is believed, were infected with the European form of typhus in childhood, but the infection remained latent for twenty or more years, long after immigration to America. In later life some circumstance permits the infection to become active and so-called Brill's disease results. I recently observed a similar example of a long latent period of kala-azar. A Chinese student had been in the United States for over six months when a typical attack of the disease occurred. Leishman-Donovan bodies were recovered from the blood and spleen, and the patient promptly recovered after treatment with an antimony preparation.

Papers given at a symposium on malaria by members of the National Malaria Committee were published in the August and September numbers of the *Southern Medical Journal*. Most of the papers were in the form of reviews of recent advances in the subject.

The Malaria Commission of the League of Nations made a study on the use of various synthetic drugs and quinine in the prevention and treatment of malaria. A report¹⁴³ of the commission contains the unanimous views of its members and practical recommendations for the treatment and prevention of the disease. Another valuable report was published by the League of Nations^{143a}.

Rickettsial Diseases—An excellent discussion of the varieties, epidemiology and geographic distribution of rickettsial diseases has been published by Zinsser¹⁴⁴ and on Rocky Mountain spotted fever by Parker^{144a}.

Diphtheria—Park¹⁴⁵ points out the difficulties inherent in deciding on the best method of immunization against diphtheria. The varying reports of the value of different procedures as found in the literature are confusing and probably result from the insufficient number of cases studied and from the use of different preparations. He outlines an ideal experiment to decide the matter. At present the best method of immunization, he believes, is the administration of two or three doses of either fluid or alum-precipitated toxoid.

143 Therapeutics and Prophylaxis of Malaria, Miscellany, J A M A **110** 1395-1397 (April 23) 1938

143a Fourth General Report of the Malaria Commission. The Treatment of Malaria, Bull Health Organ, League of Nations **6** 897 (Dec) 1937

144 Zinsser, H. The Rickettsia Diseases. Varieties, Epidemiology and Geographical Distribution, Am J Hyg **25** 430-463 (May) 1937

144a Parker, R R. Rocky Mountain Spotted Fever, J A M A **110** 1185-1188 (April 9), 1273-1278 (April 16) 1938

145 Park, W H. Duration of Immunity Against Diphtheria Achieved by Different Methods, J A M A **109** 1681-1683 (Nov 20) 1937

RARE AND "NEW" INFECTIONS OF ANIMALS AND MAN

Reports appear continually of rare or of presumably new diseases in animals and man which seem to complicate further and add to the long list of well known infections. On the other hand, certain diseases that are supposedly different, such as Oroya fever and *Verrugas peruviana*, and valley fever and coccidioidal granuloma, as described in a following paragraph, are shown to represent merely different stages of the same disease. Thus, as new methods are devised for diagnosis and new entities are delineated, the science of medicine actually becomes simplified. One questions the advisability of regarding many of the entities as "new" infections, they have probably existed unrecognized or have appeared at long intervals. It is safe to prophesy the recognition of many more infectious diseases as entities as studies are pursued further.

Whenever the discovery of a new form of micro-organism or virus in animals is announced, one immediately wonders whether or not similar forms may not be the cause of some infection in human beings of unknown origin. One is reminded of the brilliant results obtained from the studies of influenza in swine as related to influenza in human beings.

Coccidioidal Granuloma—Dickson¹⁴⁶ cites evidence to show that the puzzling condition called valley fever, as it occurs in the San Joaquin Valley in California, is actually the first stage of the disease known as coccidioidal granuloma. Among 14 patients with coccidioidal granuloma, 3 had apparently had valley fever previously. Valley fever is characterized by acute pulmonary involvement, fever, cough and sputum. It is often mistaken for pulmonary tuberculosis until the shadows are found to disappear rapidly from the roentgenograms. Erythema nodosum commonly occurs. After an interval of several weeks the symptoms of coccidioidal granuloma appear. The author suggests that the initial infection occurs in the respiratory tract and that coccidioidal granuloma is a secondary manifestation resulting from hematogenous dissemination of the fungus after a period of latency.

Epidemic Diarrhea of the Newborn—A series of outbreaks of a highly fatal unknown form of infectious diarrheal disease has affected newborn babies in hospital nurseries since 1934. In a statistical study¹⁴⁷ of 4,594 births, 711 cases of the disease are recorded, which gives a

146 Dickson, E. C. "Valley Fever" of the San Joaquin Valley and Fungus *Coccidioides*, California & West Med **47** 151-155 (Sept.) 1937, *Coccidioides* Infection, Arch Int Med **59** 1029-1044 (June) 1937.

147 Rice, J. L., Best, W. H., Frant, S., and Abramson, H. Epidemic Diarrhea of the New-Born. I. Preliminary Considerations on Outbreaks of Highly Fatal Diarrhea of Undetermined Etiology Among New-Born Babies in Hospital Nurseries, J A M A **109** 475-481 (Aug 14) 1937.

morbidity rate of about 15 per cent in the groups involved. Of these patients, 335 (47 per cent) died. Extensive study has failed to solve the problem of the etiology, and none of the usual methods of controlling epidemics has had any influence in stopping the infection. It is proposed to close nurseries and to suspend maternity services in places where infection is present in an attempt to stamp out the disease. The symptomatology, epidemiology, bacteriology, pathology and control measures are described in a paper by Best¹⁴⁸. Bundesen¹⁴⁹ contrasts the regulations proposed by Best with those applied in Chicago.

Pemphigus—Two investigators¹⁵⁰ report the development of illness and pathologic changes in irradiated mice after intracerebral inoculation of spinal fluid and fluid from blisters obtained from patients with pemphigus. The coat became rough two days after inoculation, ataxia and cachexia developed and death occurred. Histologically, necrotic areas were observed in the brain and in the meninges. The disease could be propagated by further transfer. Control animals showed no lesions.

American Trypanosomiasis—Insects infected with *Trypanosoma cruzi* were found near Los Angeles by Wood¹⁵¹. The trypanosoma which is the cause of Chagas' disease in South America was first found in San Diego County and in Arizona several years ago by Kofoid.

Some French observers¹⁵² reported an unusual infection incited by the bite of a rat. The patient's symptoms resembled those of the usual form of rat-bite fever, or sodoku, but differed in certain respects, there were sore throat, arthralgia and hydrarthrosis. A bacillus identified as *Streptobacillus moniliformis* was recovered from the blood. This bacillus occurs normally in the oral cavities of rats.

Sprochetal Jaundice—Report¹⁵³ is made of a case of infection caused by *Leptospira canicola* characterized by meningeal symptoms and apparently contracted from a Samoyed dog. An epidemic apparently caused by *Leptospira icterohaemorrhagiae* and regarded as Weil's

148 Best, W. H. Epidemic Diarrhea of the Newborn, J. A. M. A. **110** 1155-1158 (April 9) 1938.

149 Bundesen, H. N. Regulations for Prevention of Epidemic Diarrhea of the Newborn, J. A. M. A. **110** 1301-1302 (April 16) 1938.

150 Grace, A. W., and Suskind, F. H. An Agent, Transmissible to Mice, Obtained During a Study of Pemphigus Vulgaris, Proc. Soc. Exper. Biol. & Med. **37** 324-326 (Nov.) 1937.

151 Wood, S. F. A New Locality for *Trypanosoma Cruzi* Chagas in California, Science **87** 366-367 (April 22) 1938.

152 Lemierre, A., Reilly, J., Laporte, A., and Morin, M. Sur une nouvelle fièvre par morsure de rat, Bull. Acad. de med., Paris **117** 705-713 (June 22) 1937.

153 Roos, C. J., Walch-Sorgdrager, B., and Schuffer, W. A. P. Epidemic of *Leptospira Canicola* Infection in Human Subjects and Dogs, Nederl. tijdschr. v. geneesk. **81** 3324-3335 (July 10) 1937.

disease, or infectious jaundice, involved 32 of 122 students who were probably exposed by contact with contaminated holy water in fonts¹⁵⁴ Other reports of the disease have appeared from many parts of the world¹⁵⁵ Weil's disease probably occurs more frequently than is believed in the United States, and efforts should be made to diagnose the condition correctly The increase in the incidence of the disease is perhaps not due to its spread or to its actual increase but to correct diagnosis in cases in which the condition would have been mistaken for some other infection

Four cases occurred in San Francisco in March 1937 Thirty-three per cent of the rats in one community were found to harbor the spirochetes Meyer and his associates¹⁵⁶ encountered leptospiras from sick dogs in California and had difficulty in transmitting the infection to rodents The micro-organisms were classed as *L. canicola* Canine, murine and human leptospirosis, they believe, is not uncommon in California Similar findings were reported from Germany¹⁵⁷ Cases were reported from Detroit^{157a} and Brooklyn^{157b} In Scotland the disease occurs among those who handle fish^{157c} and tripe^{157d}

An unusual and hitherto unrecognized filtrable virus was encountered in rats by Woglom and Warren¹⁵⁸ during studies on rat sarcoma The virus was apparently encountered accidentally When injected subcutaneously into normal rats it causes a vigorous proliferation of connective tissue accompanied by necrosis and pus formation The infected rats seldom show any signs of systemic disease, they do not lose weight and none dies The effects are more serious after intravenous inoculation, redness, swelling and abscess formation occur in the

154 Willett, J. C., Sigoloff, E., and Pfau, C. L. An Institutional Outbreak of Epidemic Jaundice, *J. A. M. A.* **106** 1644-1646 (May 9) 1936

155 Spirochetal Jaundice, editorial, *J. A. M. A.* **109** 1128-1130 (Oct. 2) 1937

156 Meyer, K. F., Eddie, B., and Anderson-Stewart, B. Canine, Murine and Human Leptospirosis in California, *Proc. Soc. Exper. Biol. & Med.* **38** 17-19 (Feb.) 1938

157 Wirth, D. Die Leptospirose (Weilsche Krankheit) bei Tieren, *Wien klin. Wchnschr.* **50** 1115-1117 (July 30) 1937

157a Molner, J. G., and Kasper, J. A. An Outbreak of Jaundice in Detroit, *J. A. M. A.* **110** 2069-2070 (June 18) 1938

157b Glotzer, S. Weil's Disease. Report of a Case in a Fish Worker, *J. A. M. A.* **110** 2143-2145 (June 25) 1938

157c Davidson, L. S. P. Weil's Disease. New Occupational Disease in Fish Workers, *Glasgow M. J.* **11** 113 (March) 1938

157d Stuart, R. D. Leptospirosis in Glasgow Tripe Workers. Report of Possible Case of *Leptospira Canicola* Infection, *Lancet* **1** 603-606 (March 12) 1938

158 Woglom, W. H., and Warren, J. A. Pyogenic Virus in the Rat, *Science* **87** 370-371 (April 22) 1938

feet The virus could be cultivated in the chorioallantoic membrane of the chick, and it retained its virulence during three transfers

Nelson¹⁵⁹ reports an outbreak of a spontaneous disease of mice called infectious catarrh which is caused by a newly recognized micro-organism, a minute gram-negative coccobacillus, similar to that associated with fowl colyza

An infectious disease of unknown etiology was observed in Australia by Derrick¹⁶⁰ Workers in meat packing plants were involved The onset of the illness was abrupt, and the chief complaints were of malaise, headache, pains and aches in the body, anorexia and fever The face was flushed, headache was persistent, and drowsiness or stupor was common Fever lasted from seven to twenty-four days All the patients recovered When the diagnosis was being made the usual forms of known infection were ruled out by appropriate tests Guinea pigs could be infected by injecting blood or urine of a patient They were immune to reinfection No micro-organism has been recovered, but Burnet, who studied sections of tissues of animals experimentally infected, claims to have discovered rickettsia-like bodies in the spleen The disease has been named Q fever

MISCELLANEOUS

Certain interesting studies¹⁶¹ recently threw some light on the long-suspected relation between the so-called fusiform and the spiral bacteria which normally inhabit the mouth In studying colony formations of these bacteria, smooth colonies were found to be composed of short bacilli in the center, with spiral forms around the edge The spiral forms appeared to be the rough dissociant culture phases of the bacilli

Rogers¹⁶² made some interesting studies of the possible changes which occur in the blood during acute paroxysms of fever The increase in the density of the blood which precedes the fever, chill, muscle spasm, pallor and peripheral constriction was thought to be part of the anaphylactoid reaction of the fever-producing agent rather than an essential feature of the mechanism of fever itself As fever sets in there is a

159 Nelson, J B Infectious Catarrh of Mice, *J Exper Med* **65** 833-842, 843-849 and 851-860 (June) 1937

160 Derrick, E H "Q" Fever, New Fever Entity Clinical Features, Diagnosis and Laboratory Investigation, *M J Australia* **2** 281-298 (Aug 21) 1937, A New Virus Disease, *Foreign Letters, J A M A* **110** 1765-1766 (May 21) 1938

161 Tunnichiff, R, and Hammond, C Further Observations on Rough Cultures of Fusiform Bacilli, *J Infect Dis* **61** 26-30 (July-Aug) 1937

162 Rogers, F T Changes in Blood Density in Adult Man in Acute Fever Induced by Typhoid Vaccine and Malaria, *Proc Soc Exper Biol & Med* **38** 73-76 (Feb) 1938

temporary state of dilution of the blood, which returns to normal when the fever ends, especially after sweating

A report of the Metropolitan Life Insurance Company¹⁶³ shows some striking features in the decline in incidence of certain infectious diseases during the past twenty years. The following table is based on experiences among policy holders of all ages

Death Rates from Infectious Diseases, Showing the Greatest Percentage of Decline Between 1911-1915 and 1931-1935

	Percentage Decline
Typhoid fever	90.2
Malaria	87.8
Diphtheria	87.2
Diarrhea and enteritis	82.7
Measles	77.0
Whooping cough	71.7
Tuberculosis	70.2
Scarlet fever	69.2
Rheumatic fever	60.0
Erysipelas	59.3
Influenza and pneumonia	44.2

One is inclined to look for some explanation of these figures, since the incidence and mortality rates of influenza or of pneumonia, for example, in other statistics show that practically no change has occurred. It is also difficult to account for a 60 per cent reduction in death rate for rheumatic fever and erysipelas.

Application of the Langmuir Monolayer Film Technique to Biologic Problems—Shaffer and Dingle¹⁶⁴ applied Langmuir's ingenious method of measuring molecular dimensions to the study of antigens and antibodies. They found, for example, that the adsorption of type III pneumococcus carbohydrate on a polished chromium surface coated with a multiple monomolecular layer of stearate yielded a film with a maximum thickness of 50 angstrom units. Antipneumococcus type III rabbit serum when applied to such an area increased the thickness to 100 angstrom units, and antipneumococcus type III horse serum increased it to 240 angstrom units. Experiments with other types of pneumococcus antigens and antibodies suggested that in the horse the size

¹⁶³ Statist. Bull. Metropolitan Life Insur. Co. 18:3-5 (Sept.) 1937.

¹⁶⁴ Shaffer, M. F., and Dingle, J. H. A Study of Antigens and Antibodies by the Monolayer Film Technique of Langmuir, *Proc. Soc. Exper. Biol. & Med.* 38:528-530 (May) 1938.

of the antibody protein molecule or aggregate varies according to the type of the pneumococcus, as found also by using different methods, such as passage through collodion membranes or by ultracentrifugation. The film method provides a promising means for further investigation of biologic problems.

Ecker and his associates¹⁶⁵ discovered the important fact that a definite relation exists between the amount of vitamin C in the diet and the titer of complement of the serum of guinea pigs. A low complement titer resulting from vitamin C deficiency could be increased by adding crystalline vitamin C to the diet. Ascorbic acid seemed to be essential to the development of complement.

¹⁶⁵ Ecker, E. E., Pillemer, L., Wertheimer, D., and Gradis, H. Ascorbic Acid and Complement Function, *J. Immunol.* **34**: 19-38 (Jan.) 1938.

Book Reviews

A Primer for Diabetic Patients By Russell M Wilder, M D, Professor and Chief of the Department of Medicine of the Mayo Foundation, University of Minnesota Price, \$1.75 Pp 191, with 1 colored plate, 3 illustrations and many tables Philadelphia W B Saunders Company, 1937

This is an illuminating little book for any one to study who has a doubting mind about medical progress, for it depicts so well how knowledge advances

The first edition appeared in 1921, an offshoot of what the author felt was "the need for a brief outline of the principles underlying the dietary treatment of diabetes in the daily instruction of patients in the matter of their diets and hygiene" It was at first a simple affair, a mimeographed outline But the patients liked it and asked for more, and hence in due time the primer appeared in book form, attractive looking and full of common sense New editions were necessary every two or three years The popularity of the "Primer" is a good indicator of the fact that patients with diabetes wish to keep abreast of the times and try to be a jump or two ahead of their disease Each new edition was a little larger, a little more pretentious and a little fuller of information than its predecessor, but equally well liked The first edition was 76 pages long the second 119, the fourth 138 and the fifth 172, and now the sixth has 191 pages to its credit It probably is no exaggeration to say that the diabetic patient in 1938 must know twice as much about his illness in order to remain well as he did in 1921 and that there is twice as much knowledge available for him to acquire Now, in addition to everything else that he must be taught in regard to diets, urinalyses and the prevention of coma and gangrene, he must learn about protamine zinc insulin, how to use it and how it differs from old insulin All this is told in the new "Primer" with charming simplicity and honesty

A sister of the ARCHIVES, *The Journal of the American Medical Association* (J A M A 82 572 [Feb 16] 1924, 96 553 [Feb 14] 1931, 103 1976 [Dec 22] 1934), on several occasions has had nice things to say about the "Primer" The ARCHIVES, too, would like to praise it For, as unpretentiously as ever, the "Primer" continues to be what it started out as a brief, well written, authoritative outline of the principles underlying the modern treatment of diabetes expressed in easily understood English Doctor as well as patient should read it, lest the patient on visiting the doctor demonstrate that of the pair he is the more alert and better educated diabetically

The Larynx and Its Diseases By Chevalier Jackson, M D, and Chevalier L Jackson, M D Price \$8 Pp 555, with 220 illustrations, including 11 colored plates Philadelphia W B Saunders Company, 1937

This book will receive and certainly deserves a hearty welcome from the members of the medical profession in this country Those interested in laryngology in particular have looked forward to its publication It is the only textbook of recent years devoted exclusively to the diseases of the larynx As the authors say in their preface, "This is remarkable when one considers the prevalence of laryngeal disease"

The book itself is not too voluminous, and it does not tire one with insignificant details Essentially, it is a clear, concise review of all the diseases peculiar to the larynx In addition, it contains a full chapter relative to the laryngeal phases of general disease In this respect, and in many others too numerous to mention, the book should be a valuable adjunct to the library of the general practitioner

The varied phases of laryngeal disturbances are thoroughly presented in an orderly fashion For each disease the authors give the definition and then present the incidence, etiology, pathology, laryngeal appearance, symptomatology, diagnosis, complications, treatment, prognosis and sequelae and a historical note The

last four chapters are devoted to the description of laryngeal and endolaryngeal operative procedures

There are two hundred and twenty illustrations, including eleven plates in color, all of which were drawn by Dr Chevalier Jackson

All recent advances have been incorporated in this volume. It represents the current ideas in laryngology and will do much to bring forth more accurate diagnoses and a better understanding of methods of treatment. As a practical and useful textbook, this volume cannot be too highly praised

Practical Proctology By Louis A. Buie, M.D., Professor of Proctology, the Mayo Foundation. Price, \$6.50. Pp. 512, with 152 illustrations. Philadelphia: W. B. Saunders Company, 1937.

This book is written with gusto and is a fine, enthusiastic achievement. It bears the hallmarks of Mayo Clinic efficiency. It is based on ten years' work in a most active medical center and on a personal experience of over forty thousand proctoscopic examinations. Needless to say, it is well printed and clearly illustrated.

Its title gives the clue to the character of the volume. It is not a treatise for the specialist, but, on the other hand, it is the kind of practical book that any internist will enjoy reading. It will make him realize that he can learn proctoscopic technic, that such examinations are important and that without ability to examine the lower portion of the bowel properly he is an unfinished diagnostician.

There is an excellent bibliography at the close of each chapter. Sensible diet lists are appended that may be useful in the treatment of intestinal conditions requiring high or low residues. There are practical prescriptions of one kind or another for palliative therapy as well as descriptions of formidable-sounding operative procedures that are now familiar to the expert proctologist.

In brief, one can here obtain a bird's-eye view of what modern proctology is, and if one wishes detailed information in any specific phase of the subject, the information is at hand, clearly expressed and always based on a palatable combination of experience and knowledge of the literature. On the whole, the book is admirable.

The Cerebrospinal Fluid By H. Houston Merritt, M.D., and Frank Fremont-Smith, M.D. With a foreword by James B. Ayer, M.D. Price, \$5. Pp. 333, with 17 illustrations and 63 tables. Philadelphia: W. B. Saunders Company, 1937.

This is a well assembled monograph. As Dr. Ayer states in the foreword, its purpose is to present facts—facts based on thousands of examinations of spinal fluid made under standard conditions in connection with a variety of diseased states in the wards and in the laboratory of the Boston City Hospital.

The book is written in a scholarly fashion, and due respect is paid to the literature. Nearly eight hundred references are mentioned which have been assembled since Quincke began the clinical examination of spinal fluid, in 1891. And so, throughout the entire volume, the writers compare their own experience with that of others and build up a notably comprehensive and reliable account of the present position of this particular laboratory test as a part of the diagnostic armamentarium.

The book is easily read as it is well and clearly written. The technic is clearly described, not merely the technic of how to withdraw spinal or cisternal fluid and how to measure the pressure properly, but also the technic of roentgenography of the ventriculosubarachnoid space (by Dr. T. J. C. von Storch) and the technic of cell counting and chemical determinations of the spinal fluid. The latter subjects were written about by Miss Mary D. Irvine, who must have had vast experience with these methods.

On the whole, here is a successful effort. It is an up-to-date account of the spinal fluid and will soon become a useful handbook in all hospitals and medical schools.

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LIPOID NEPHROSIS

A STUDY OF NINE PATIENTS, WITH SPECIAL REFERENCE TO
THOSE OBSERVED OVER A LONG PERIOD*

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MILWAUKEE

A problem of fundamental importance in the clinical study of any form of Bright's disease is a consideration of the length of time the patient has been observed. This is particularly true in the study of lipoid nephrosis because a diagnosis cannot be made with any degree of certainty without a long period of observation. Too often a patient is studied during one stage of the disease, and the signs and symptoms observed in this brief period are considered to constitute the true picture of the renal disorder. In chronic glomerulonephritis the variability of the clinical features often leads to confusion in their proper interpretation. At one time all the major symptoms—albuminuria, edema, hypertension, nitrogen retention and occasionally a convulsion—may be present. Later, hypertension and nitrogen retention may disappear and albuminuria and edema may be so pronounced that lipoid nephrosis is thought to exist. At another stage of the disease there may be no edema, but hypertension, hematuria and retinopathy may furnish sufficient evidence for a diagnosis of chronic glomerulonephritis.

One of the main obstacles to the proper identification of lipoid nephrosis has been the failure to study patients carefully over a long period. Most cases that are loosely called cases of lipoid nephrosis are examples of chronic glomerulonephritis with extensive lipoid degeneration of the tubules. Even in some published reports it is seen that

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the blood pressure later rose and genuine uremia developed. In our opinion these were not cases in which lipoid nephrosis developed into chronic glomerulonephritis but were cases of chronic nephritis from the beginning. The confusion that has existed because chronic glomerulonephritis may be characterized by edema is beginning to disappear. Observations have convinced us that in the course of chronic nephritis there may be periods lasting from weeks to months in which the nephrotic syndrome dominates, yet further study proves conclusively that the case is one of chronic glomerulonephritis with secondary lipoid nephrosis.

In an attempt to draw a line of differentiation between the apparently degenerative and the evidently inflammatory renal lesions, Mueller¹ in 1905, proposed the term nephrosis for the primary degenerative diseases. This distinction was not accepted without considerable criticism especially from such German pathologists as Lohlein² and Aschoff,³ but later this term was popularized by Munk⁴ and Volhard and Fahr⁵. The nephroses, according to Munk's classification, include several types of degeneration of the renal tubules. For example, there are (a) albuminous degeneration, (b) fatty degeneration, (c) hyaline degeneration, (d) amyloid degeneration, (e) glycogen degeneration, as seen in diabetes mellitus, and (f) lipoid nephrosis. It is the type called lipoid nephrosis by Munk, genuine nephrosis by Volhard and Fahr⁵ and chronic nephrosis by Epstein⁶ that is the problem for discussion here. Clinicians, particularly Christian,⁷ of this country, and Gainsborough,⁸ of England, and pathologists, notably Bell⁹ and Shaw Dunn,¹⁰ have refused to accept the condition as anything more than a phase of glomerulonephritis. Recent work, especially that by Randerath¹¹ and

1 Mueller, F. Morbis Brightii, Verhandl d deutsch path Gesellsch **9** 64, 1905

2 Lohlein, M. Ueber Fettinfiltration und fettige Degeneration der Niere des Menschen, Virchows Arch f path Anat **180** 1, 1905

3 Aschoff, L. Ueber den Begriff der "Nephrosen" und "Sclerosen," Deutsche med Wchnschr **43** 1345, 1917

4 Munk, F. Die Nephrosen, Med Klin **12** 1019, 1916

5 Volhard, F., and Fahr, T. Die Brightsche Nierenkrankheit. Klinik Pathologie und Atlas, Berlin, Julius Springer, 1914

6 Epstein, A. A. Concerning the Causation of Edema in Chronic Parenchymatous Nephritis. Method for Its Alleviation, Am J M Sc **154** 638, 1917

7 Christian, H. A. Nephrosis. A Critique, J A M A **93** 23 (July 6) 1929

8 Gainsborough, H. Study of So-Called Lipoid Nephrosis, Quart J Med **23** 101, 1929

9 Bell, E. T. Lipoid Nephrosis, Am J Path **5** 587, 1929

10 Dunn, J. S. Nephrosis or Nephritis? J Path & Bact **39** 1, 1934

11 Randerath, E. Die Entwicklung der Lehre von der Nephrosen in der pathologischen Anatomie, Ergebn d allg Path u path Anat **32** 91 1937

Fahr,¹² has exemplified the changing conception of the relation between the two diseases. The idea is growing that lipoid nephrosis is distinct and that hyperpermeability of the glomerular capillaries without demonstrable damage to the capillary walls leads to the morphologic changes seen in the tubular epithelium and glomeruli. If the confusion that has arisen between lipoid nephrosis and other forms of Bright's disease is to be overcome, it is essential to identify its characteristic features by prolonged observations and with great precision.

Our purpose in reporting this series of cases is to show by extended clinical study and histologic examination that lipoid nephrosis is essentially distinct from chronic glomerulonephritis with the nephrotic syndrome and that there is justification on clinical grounds alone for retaining the term. Apart from the argument over the identity of lipoid nephrosis, it is thought that to establish it as an entity may arouse more active investigation into the cause of the hyperpermeability of the glomeruli for albumin, the production of edema and the abnormal metabolism of cholesterol. However, it is not our aim to solve the problem of the functional changes around which the excessive albuminuria and edema revolve. A clinical study of the 9 cases presented here, with a careful and prolonged follow-up study of some of them and an examination of the histologic changes in others, may help to clarify some aspects of the controversy.

The histologic examination of the kidney in so-called lipoid nephrosis shows how the confusion has arisen. Frequently there has been a lack of correspondence between the clinical and the pathologic features, and at autopsy patients with supposed lipoid nephrosis have been found to have chronic glomerulonephritis. In such instances the period of clinical study has usually been too short for a correct diagnosis. Often when the kidney fails to show the classic histologic picture of chronic glomerulonephritis, special stains reveal minimal glomerular changes. These are considered by some to be inflammatory changes and by others degenerative. However, this difference of opinion does not lessen the importance of the fundamental fact that patients with such renal changes have a course that is very different from that of patients with true glomerulonephritis.

The clinical and histologic features of lipoid nephrosis have recently been surveyed so comprehensively by Leiter¹³ that further amplification is hardly necessary now. Furthermore two of us¹⁴ (Dis Murphy

12 Fahr, T, in Henke, F, and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1934, vol. 6, pt. 2, p. 829.

13 Leiter, L. *Nephrosis, Medicine* **10** 135, 1931.

14 Murphy, F. D., and Warfield, L. M. *Lipoid Nephrosis, Arch. Int. Med.* **38** 449 (Oct.) 1926.

and Warfield) have discussed the disease fully in a previous report. In brief, it is identified clinically by both positive and negative features. There are marked albuminuria, hypercholesterolemia, edema and doubly refractive lipoids in the urine, but just as important are the lack of hypertension, nitrogen retention and genuine uremia and the freedom from an abnormal number of red blood cells in the urinary sediment. Any indications of cardiovascular changes, such as cardiac hypertrophy, arteriosclerosis or albuminuric retinitis, are conspicuously absent. Reduction of the plasma protein content, particularly a deficit of plasma albumin caused by the marked albuminuria, has come to be looked on as an important clinical feature. The course of lipid nephrosis extends over a period of months to several years and frequently terminates in complete recovery. Occasionally during the periods of extreme edema a secondary infection, often pneumococcal, develops and causes pneumonia or pneumococcal peritonitis.

REPORT OF CASES

In this report 9 cases which fulfil the rigid requirements for a diagnosis of genuine lipid nephrosis are discussed. Cases 1 to 3 were reported in an article published in 1926.¹¹ Two patients (cases 2 and 3) have been observed periodically since that time and an after-study is given here. Two of the 9 patients died and were studied post mortem. 6 recovered completely and 1 is under observation at present.

CASE 1—A man aged 21 entered the hospital on Oct. 27, 1924, complaining of headache and swelling of the legs. The past history was unimportant except for scarlet fever at the age of 10 and gonorrhea at 20.

Physical examination revealed a well built, well nourished, pale man with considerable edema of the legs, face and eyelids. The lungs, heart, abdomen and eyegrounds were normal. There was no dyspnea. The blood pressure was 118 systolic and 70 diastolic, and the blood vessels were soft. The reflexes were normal.

Urinalysis showed considerable albumin, no red blood cells, a few leukocytes, hyaline casts and many doubly refractive lipoids. Chemical examination of the blood showed 500 mg. of cholesterol per hundred cubic centimeters. The serum looked milky. The Wassermann reaction was negative. The phenolsulfonphthalein test showed 60 per cent excretion in one hour. The blood count was normal. The basal metabolic rate ranged between -10 and -15 per cent.

While the patient was under observation in the hospital the edema fluctuated, reaching a degree so severe at times that the skin cracked, during such periods he became semicomatose. These fluctuations apparently had no relation to treatment, although large doses of thyroid seemed to prolong the interval between attacks. During the attacks the urea nitrogen and the creatinine content of the blood remained normal, but the cholesterol content rose. The albuminuria remained marked at all times. The patient died eighteen months after admission to the hospital. Partial necropsy was performed.

Gross Postmortem Description—There was a small amount of clear, yellow fluid in the peritoneal cavity, and the tissues were slightly edematous. The

kidneys were large, firm and pale. The capsule stripped with ease leaving a smooth, pale surface which was mottled creamy white and pink. The cortex was a creamy white and was greasy in appearance. It measured 12 to 14 mm in thickness and was well marked off from the pyramids. The pelves appeared normal.

Microscopic Postmortem Description—The glomeruli showed no signs of inflammatory change. The proximal convoluted tubules revealed extensive and profound degenerative changes. The cells were pale and swollen, and the nuclei were often not visible. The protoplasm looked granular and the lumens of the tubules were filled with granular debris. There were doubly refractive lipoids in the tubular epithelial cells. The collecting tubules and small arteries showed no definite changes. The adrenal glands, spleen, liver and heart were normal in appearance. On section the liver was pale, edematous and moderately congested. The heart showed a slightly raised, yellowish area in the aortic leaflet of the mitral valve. The abdominal aorta showed numerous yellowish, elongated areas slightly raised above the surface, as well as small rounded, button-like areas. Sections of the aorta through one of the yellow patches showed characteristic lesions of atheroma in the intima. Many refractive lipoids were present.

CASE 2—A woman aged 25, a stenographer, began to have headaches and puffiness of the face and ankles in 1921. Urinalysis at that time showed marked albuminuria, a few white blood cells, an occasional cast but no red blood cells.

In 1922 a more complete examination was made. The heart and lungs were normal. The edema, which had come and gone during the last year and a half, was marked. The blood pressure was 122 systolic and 84 diastolic. The Wassermann reaction of the blood was negative. The blood counts were normal. Renal function tests revealed no insufficiency.

During 1923 and 1924 the edema and headaches fluctuated, and the quantity of albumin in the urine varied considerably. The blood pressure remained normal. During this time the patient continued to work.

Urinalysis on Dec 5, 1925, showed 2 plus albumin, a specific gravity of 1.024, no red blood cells, a few pus cells and many doubly refractive lipoids. Chemical examination of the blood showed nonprotein nitrogen, normal, and cholesterol, 384 mg per hundred cubic centimeters. Various diets and treatments, including the use of thyroid, were given, but no therapeutic agent seemed to have much influence.

This patient has been under observation from time to time until the present. Since 1925 there has been no edema. The albuminuria subsided, and there has been no recurrence. She is working regularly and appears to have recovered completely from the lipoid nephrosis.

CASE 3—A man aged 24 entered the hospital on Dec 9, 1925, complaining of swelling of the ankles and face, headache and loss of appetite. The symptoms developed two months before entry without apparent cause. They subsided after some treatment but returned. The past history was unimportant except that he had gonorrhea at the age of 18.

Physical examination revealed considerable edema of the legs and face. The heart, lungs and liver were normal. The blood pressure was 125 systolic and 75 diastolic. The Wassermann reaction was negative. The eyegrounds were normal.

Urinalysis showed 4 plus albumin, no red blood cells and many doubly refractive lipoids. Chemical examination of the blood showed 666.6 mg of cholesterol per hundred cubic centimeters. The basal metabolic rate averaged +10 per cent.

The edema fluctuated in intensity and at times became so pronounced that the patient was confined to bed for a number of weeks. The marked albuminuria persisted. After March 1, 1926, the edema disappeared entirely and never returned. For a number of months there was moderate albuminuria, which gradually diminished until about April 1927, when only a trace of albumin was found in the urine. He was reexamined in 1931 for the purpose of presentation at a clinic and was apparently perfectly normal at that time. In May 1937 he was examined again and, as the chart shows, was found to be normal in every respect.

CASE 4—A woman aged 32, entered the hospital on Jan. 24, 1925, for the treatment of generalized anasarca. The past history was unimportant except for diphtheria at the age of 8 years and the infections of the upper respiratory tract that are common in childhood. The present symptom came on slowly and painlessly without apparent cause in September 1924. The edema was intermittent for several months. There were no other complaints.

Physical examination at the time of the patient's entrance into the hospital revealed pronounced generalized anasarca. The heart was normal, and the blood pressure was 130 systolic and 80 diastolic.

Urinalysis showed 4 plus albumin, a specific gravity of 1.017, an occasional red blood cell, 2 or 3 pus cells, 2 to 4 hyaline casts and many doubly refractive lipoids. Chemical examination of the blood showed nonprotein nitrogen, 26.6 mg; urea nitrogen, 11.1 mg; creatinine, 2.2 mg; and cholesterol, 490 mg, per hundred cubic centimeters. Renal function tests showed phenolsulfonphthalein, 50 per cent excreted in the first hour and 25 per cent in the second, dilution and concentration, 1 to 1.022.

The edema fluctuated during the spring of 1925, and in May it disappeared entirely. The albuminuria persisted during 1926 and 1927, but there was no further recurrence of edema. The patient was last seen on Aug. 10, 1934. At that time she was perfectly normal except that there was a trace of albumin in the urine.

CASE 5—A man aged 18, a truck driver, entered the hospital on July 25, 1930. He complained of edema and oliguria which had lasted for twelve weeks. He had been in good health before that time. The swelling began in the face and spread over the entire body. Some pain and dyspnea were associated with it.

The patient had had mumps, measles, influenza and gonorrhea. The family history was unimportant.

Physical examination revealed a well developed, pale, pasty-looking boy who was so edematous that he lay on his back and had difficulty in moving. The pharynx was injected, and the tonsils were enlarged. The lungs and the heart were normal. The blood pressure was 112 systolic and 70 diastolic. There were draining perforations and many bullae in the right lower portion of the abdomen. The extremities were greatly swollen, and there was diffuse vesiculation over the lower portion of the abdomen and the thighs.

Urinalysis showed 4 plus albumin, a specific gravity of 1.018, 4 to 5 white blood cells, 1 or 2 red blood cells, no casts and many doubly refractive lipoids. Chemical examination of the blood showed cholesterol, 584.6 mg; chlorides 364 mg; total protein, 3.75 Gm; albumin, 1.61 Gm; and globulin, 2.14 Gm, per hundred cubic centimeters. A blood count showed hemoglobin, 70 per cent; red blood cells, 3,420,000; and white blood cells, 19,950. The renal function tests gave normal results.

During his stay in the hospital the patient had a series of severe infections. In September 1930 he had pneumonia followed by empyema. In October he had

erysipelas and after a prolonged course gradually recovered. In November the edema and albuminuria had completely disappeared. He made a complete and uneventful recovery.

This patient returns twice a year. Examination in August 1937 showed the urine, heart and blood pressure to be normal. He appeared to have recovered completely.

CASE 6—A girl aged 7 years was admitted to the hospital on Dec. 19, 1935. One week before entrance, edema developed in the face, abdomen and extremities. A year and a half before entry she had a similar attack, which lasted several weeks. Both parents had chronic nephritis. The patient had had whooping cough, pneumonia, chickenpox and measles.

Physical examination revealed a well developed, well nourished and very edematous girl. The heart and lungs were normal. The eyegrounds were normal. The blood pressure was 120 systolic and 60 diastolic.

Urinalysis showed 4 plus albumin, a specific gravity of 1.025, an occasional red blood cell, 3 to 4 white blood cells and no casts. Chemical examination of the blood showed cholesterol 530 mg, total protein, 3.93 Gm, albumin, 1.49 Gm, and globulin, 2.44 Gm per hundred cubic centimeters. The blood counts were normal, and the sedimentation rate was rapid.

The output of fluid was low, but it gradually increased during the course of treatment. The edema disappeared, and the patient's condition became so satisfactory that she was discharged six weeks after entrance.

The patient was last examined on Aug. 11, 1937. She was free from all evidences of renal disorder and appeared to be in good condition.

CASE 7—A man aged 34, was first seen on April 19, 1932. He had always been well and had worked as a railroad switchman until about four months prior to entry, when he began to notice that his ankles and face, especially around the eyes, were swollen in the morning when he arose. For a number of weeks the swelling had disappeared after several hours of activity. Then the edema became more pronounced and failed to subside. During March and April he was so edematous that he was unable to get out of bed.

The family history was irrelevant and the patient's past history was uneventful except for measles at the age of 9 years and numerous attacks of infection of the upper respiratory tract.

Physical examination revealed a well developed and strong man whose only difficulty was generalized anasarca. The heart, lungs, abdomen and eyegrounds were normal. The blood pressure was 132 systolic and 80 diastolic. There was no arteriosclerosis.

Urinalysis showed 4 plus albumin, an occasional red blood cell, numerous hyaline casts and many doubly refractive lipoids. Chemical examination of the blood showed cholesterol, 484 mg, nonprotein nitrogen, 36.6 mg, creatinine, 1.6 mg, total protein, 4.92 Gm, albumin, 1.8 Gm, and globulin 2.95 Gm, per hundred cubic centimeters. A phenolsulfonphthalein test showed 75 per cent excretion in two hours. Except for signs of mild anemia the blood count was normal. The Wassermann reaction was negative.

In May 1933 the edema gradually subsided. Albuminuria and some edema about the face and ankles persisted during the entire summer of that year. Sometime early in the fall of 1933 the albuminuria disappeared and never returned. The cholesterol content of the blood dropped to 260 mg per hundred cubic centimeters and the albumin-globulin ratio returned to normal.

Observations made on this patient during 1935, 1936 and 1937 showed no evidences of renal disorder. The patient has worked steadily since 1933 and has had no ill effects from the disease.

CASE 8—The patient, a boy aged 3 years, was admitted to the hospital on May 25, 1937. Two months before entrance there was a gradual onset of generalized edema. No sign of infection of the upper respiratory tract was noted before the edema developed, and there were no convulsions. The past history showed none of the usual diseases of childhood, and the patient had not been subject to infections of the upper respiratory tract.

Physical examination revealed a fairly well developed pale boy. There was marked pitting edema involving the entire body. The abdomen was distended with fluid. The blood pressure was 100 systolic and 78 diastolic. Otherwise there were no significant findings.

Urinalysis showed 4 plus albumin, a specific gravity of 1.017, 2 to 3 white blood cells and no red blood cells. Chemical examination of the blood showed cholesterol, 416.6 mg, total protein, 4.98 Gm, albumin, 3.12 Gm and globulin, 1.86 Gm, per hundred cubic centimeters. Seventeen grams of protein was excreted in twenty-four hours. The sedimentation rate was 100 mm in one hour. Renal function tests gave practically normal results.

The patient became very edematous. Marked distention of the abdomen followed and fever developed. A diagnosis of pneumococcic peritonitis was made. The temperature rose to 103 F. The patient became comatose and died on June 10.

The primary cause of death as determined at autopsy was generalized pneumococcic peritonitis and the contributory cause was lipoid nephrosis.

Gross Postmortem Description—The right kidney measured 10.5 cm in length, 5 cm in width and 3 cm in thickness and weighed 90 Gm. The capsule stripped easily, exposing a pale external surface, on which the stellate veins were extremely dilated. On cut section the parenchyma appeared to be pale yellow. It averaged about 20 mm in thickness, of which 7 mm was cortical tissue. The markings of the kidney were absent, and there was only a bright red streaking of the medullary portion. The pelvis showed a slightly congested mucous membrane and emptied into two ureters, which fused about at the level of the lower pole of the kidney into a single ureter.

The left kidney measured 10 cm in length, 5 cm in width and 3 cm in thickness and weighed 80 Gm. The gross appearance of the left kidney externally was much the same as that of the right. On cut section the parenchyma averaged 20 mm in thickness of which 5 mm was cortical tissue. The gross structure on the cut surface was essentially the same as that of the right kidney. Both kidneys were of doughy consistency.

Microscopic Postmortem Description—The glomeruli studied in various sections were fairly normal in appearance. In a few, however, there was a slight proliferation of epithelial cells. Sections studied with the azocarmine stain showed no definite thickening of the basement membrane of the capillaries. There was no deposit of fatty substance within the glomeruli. The convoluted tubules showed swollen, granular and vacuolated epithelial cells, which in general appeared lightly stained. Some of the epithelial cells lining the tubules showed extensive swelling and in some of them the nuclei could not be recognized. In some areas the epithelial cells of the convoluted tubules showed an increased number of mitotic figures. Sections stained for fat revealed an accumulation of minute droplets of fat in the basal portion of the epithelial cells. This deposit was not uniform and was not seen throughout all the tubules. On examination with the polarizing microscope this fat was anisotropic. The lumen of the tubules contained granular amorphous material. In other areas some of the tubules contained a homogeneous colloid-like

substance. The interstitial tissue of the kidney was free from cellular infiltration. The veins of the interstitial tissue were somewhat congested. The arteries showed no abnormal thickening or sclerotic processes.

CASE 9—The patient, a boy aged 3 years, entered the hospital in December 1935, suffering from generalized anasarca. The edema, which began in September, came and went but gradually became worse until, on the day of entrance, he was too edematous to walk.

Physical examination revealed a well developed and well nourished boy. The heart and lungs were normal. The abdomen was distended with fluid, and the eyelids, extremities and genitalia were badly swollen.

Urinalysis showed 4 plus albumin, a specific gravity of 1.034, no red blood cells, several pus cells, granular casts and many doubly refractive lipoids. Chemical examination of the blood showed cholesterol 503 mg, nonprotein nitrogen, 247 mg, plasma protein, 3.08 Gm, albumin, 1.37 Gm, and globulin, 1.71 Gm per hundred cubic centimeters. Except for evidence of mild secondary anemia the blood counts were normal.

The edema disappeared after three months of treatment in the hospital. In April the patient returned home and was free from edema during the spring and summer of 1936. Moderate albuminuria persisted.

On Oct. 16, 1936, he was so edematous that hospitalization was again necessary. Physical examination showed no deviation from the former record. Urinalysis revealed marked albuminuria, a specific gravity of 1.024, no red blood cells, a few pus cells, a few casts and many doubly refractive lipoids. Chemical examination of the blood showed cholesterol, 608 mg, nonprotein nitrogen, normal content, total protein 2.97 Gm, albumin, 1.60 Gm, and globulin, 1.07 Gm, per hundred cubic centimeters.

The patient remained under observation in the hospital for some time. The marked albuminuria persisted for several weeks. The edema fluctuated in intensity during 1937. At present it has disappeared, and the patient appears to be recovering.

ANALYSIS OF CLINICAL DATA

Although lipoid nephrosis may occur at any age, it is rare after the age of 40 and develops most frequently in children and adolescents. The ages of the patients in this series ranged from 3 to 34 years, 6 were between 17 and 34 years of age, and 2 were 3 years old. There were 6 males and 3 females. There was no correlation between the age of the patient and the outcome of the disease. The first patient was aged 21 and died of a convulsion, with generalized edema, while the eighth patient was aged 3 and died of pneumococcal peritonitis. It may be that resistance to pneumococcal infection is lower in children than in adults. In no case was the etiologic factor definitely established. A summary of the essential data in these cases is given in table 1.

In no case was there the acute abrupt onset described by Blackman¹⁵ and others. The disorder apparently began insidiously with edema of the face and ankles and gradually developed into generalized anasarca.

15 Blackman S. S. J. Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis. Clinical and Anatomical Studies. Bull. Johns Hopkins Hosp. 55:1, 1934.

TABLE 1—Summary of Clinical Data

Case No	Patient's Initials, Date	Age	Urine				Edema	Blood				Renal Function				Comment		
			Albumin	Specific Gravity	Red White Blood Cells			I pords	Mm Hg	Urea Nitro- gen, Mg per 100 Ce	Creat- inine, Mg per 100 Ce	Chols- terol, Mg per 100 Ce	Non- protein Nitro- gen, Mg per 100 Ce	Albu- min Glob- ulin Ratio*	Phenol sulphon- phthal- ein Test, % in 2 Hr		Dilution and Concen- tration Test	Urea Clear- ance Test, %
1	J H																	
	10/24/24	21	++++	1.023	0	Few	Few	++++	110/60	22.0	1.5		25.6		50	1.003.1.025		
	12/ 1/25	22	++++	1.025	0	Few	Few	++++	120/75	20.0	2.3	806.0	30.9		65	1.005.1.027		
	2/10/26	23	++++		0			++++	120/70	16.8	1.7	555.0	28.5		55	1.003.1.027	Died	
2	H Z																	
	11/ 7/22	25	++		0	Few	Hyaline	0	120/80	16.8	1.4		31.6		65	1.002.1.028		
	12/ 5/25	28	++	1.021	0	Few	0	++	116/75	18.0	1.8	84.0	29.7					
	0/21/30	33	0		0	0	0	0				188.0						
	11/23/35	38	0		0	0	0	0										
	8/ 5/37	40	0		0	0	0	0	132/80							1.004.1.026	41.6 Recovered	
3	F K																	
	12/ 9/25	24	++	1.020	0	Few		++	125/75	18.0	1.7	666.6	42.5		60	1.006.1.070		
	1/19/26	25	++	1.018	0	0	0	++	130/80	12.0		744.0			75			
	3/ 1/26	25	++	1.022	0	0	0	0	115/80	20.0	1.9	588.0						
	11/ 7/31	31	0		0	0	0	0	120/80			180.0			65		43.5 Recovered	
	5/22/37	37	0	1.021	0	0	0	0	122/70									
4	S M																	
	1/24/25	32	++++	1.010	0	1.2	Occa- sional hyaline	++	118/60	14.0	2.7	762.9	32.7		55	1.001.1.022		
	6/ 0/27	34	+	1.007	0	0	0	+	110/70	23.8	1.7	196.0	36.1	T.P., 6.00 Alb., 4.40 Glob., 2.78	75	1.003.1.021	40.8 Recovered	
	8/10/34	41	+	1.020	0	0	0	0	120/80									
5	C L																	
	7/26/30	18	++++	1.015	1.2	45	0	++	112/70	18.2	1.4	718.6	31.5	T.P., 3.75 Alb., 1.61 Glob., 2.07	40	1.005.1.010		
	9/ 9/30	18	++	1.025	0	0	0	0	103/75	26.6	1.9	211.0	37.0	T.P., 6.07 Alb., 4.00 Glob., 2.07	65	1.002.1.025		
	10/30/30	18	0	1.021	0	0	0	0	110/62						55	1.001.1.022	Recovered	
	8/ 2/37	25	0	1.025	0	0	0	0	110/70									

6	D S	7	++	+++	1025	12	34	0	++++	122/68	++++	168	16	5300	334	T P, 39; S0 Alb, 149 Glob, 214	1001100	113
	12/21/35	7	++	+++	1025	12	34	0	++++	122/68	++++	168	16	5300	334	T P, 39; S0 Alb, 149 Glob, 214	1001100	113
	2/18/36	8	++	+++	1015	23	0	0	++	105/70	0	154	15	3333	277	T P, 114 S0 Alb, 204 Glob, 200	10021027	1251
	3/3/36	8	++	+++	1020	23	0	0	++	100/80	0	140	15	2777	282	T P, 115 75 Alb, 280 Glob, 235	10081028	
	6/23/37	9	0	+++	1026	1	23	0	0	100/60	0					T P, 724 Alb, 410 Glob, 255	10101026	
	8/11/37	9	0	+++		0	0	0	0		0							
7	H C																Recovered	
	1/9/32	34	++	+++	1022	Occ	34	Hyaline	++++	132/80	++++		16	4810	368	T P, 402 75 Alb, 180 Glob, 295	10061028	
	6/1/33	15	+	+++	1020	0	0	0	0	130/80	0			2000		T P, 680 65 Alb, 400 Glob, 250		
	10/23/35	37	0	+++	1024	0	0	0	0	136/84	0							
	7/10/37	39	0	+++		0	0	0	0		0							
8	A P																Recovered	
	5/27/37	3	++	+++	1017	0	23	0	++	100/78	++	110	13	1166	277	T P, 498 Alb, 312 Glob, 186		
	6/1/37	3	++	+++	1035	0	23	Many, granular	++++	115/84	++++	188	13	3528	297	T P, 431 Alb, 198 Glob, 235		
	6/8/37	3	++	+++	1017	0	23	Many, granular	++++	105/80	++++	258	16	3816	461	T P, 150 Alb, 240 Glob, 210		
9	A S																Died of pneumo coccal peritonitis	
	12/10/35	3	++	+++	1031	0	0	Tew	++		++			5030				
	1/8/36	3	++	+++	1024	0	78	Many, granular	++++	100/60	++++			6080	217	T P, 308 Alb, 137 Glob, 171	10081030	
	12/21/36	3	++	+++		12	34									T P, 297 Alb, 160 Glob, 107		
	6/9/37	1	++	+++	1026		Tew											Progress satisfactory

* T P indicates total protein Alb, albumin Glob, globulin

The results of chemical examinations of the blood and other laboratory data are tabulated in table 1. These results conform to data published regarding other cases of lipoid nephrosis. Hypercholesterolemia, inversion of the albumin-globulin ratio and the absence of nonprotein nitrogen or of creatinine retention were features of every case. The ability to concentrate was normal, and no insufficiency was found with the phenolsulfonphthalein or the urea clearance test. In no instance was there arteriosclerosis of the peripheral arteries, hypertension, retinitis or cardiac hypertrophy. The Wassermann reaction was negative in all cases.

Albuminuria was marked, the amount of albumin excreted varying from 5 to over 45 Gm. a day during the active period of the disease. This excessive loss of albumin was closely related to the deficit of plasma protein and the onset of edema. The specific gravity of the urine was high, ranging from 1.017 to 1.035. The urinary sediment in no case contained more than an occasional red blood cell, but white blood cells and waxy casts were common features. Doubly refractive lipoids were found with the polarizing microscope in every case, but the number and size bore no relation to the degree of edema. It was not uncommon to find them in the urine months after the edema had subsided. When albuminuria disappeared, anisotropic lipoids were not in evidence.

The outstanding feature was the edema which followed practically the same pattern in every case. It came on gradually and painlessly and within a few weeks disappeared without causing the patient much discomfort, only to return weeks or months later. The recurrent attacks were more severe and resistant to treatment than the original ones and in some cases the swelling assumed tremendous proportions. Although edema is a constant feature, it must be borne in mind that it is intermittent. Many believe that this symptom constitutes lipoid nephrosis but the disease may persist for many years, as is seen from observations recorded here, and yet edema may be prominent for only a short period.

Examinations of the protein content of the blood plasma were made in all cases except cases 1 to 3. The onset and remissions of attacks of edema were closely related to changes in the plasma protein content. In case 4 a determination of the quantities of total protein and albumin was not made during the period of edema. Our observations are in accord with the view of Moore and Van Slyke,¹⁶ who have pointed out that patients with a low plasma protein content show a tendency to

16 Moore, N. S., and Van Slyke, D. D. The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J. Clin. Investigation* 8: 337, 1930.

edema formation. Our examinations show that there is no exact parallelism between the onset of edema and the decrease of the plasma protein content. This is particularly emphasized in case 8. The lack of correspondence is undoubtedly due to the fact that the colloidal osmotic pressure of the blood plasma does not always conform to the changes in the quantity of plasma protein.

Hypertension was not observed during the course of the disease. When in a case considered at first to be one of lipid nephrosis hypertension developed, even though mild in type, other symptoms of chronic glomerulonephritis invariably followed.

From the clinical point of view the study of these cases over a number of years has led to an understanding of the true course and outcome of lipid nephrosis that cannot be afforded by short periods of observation. One patient (case 2) was studied for fifteen years, 2 (cases 3

TABLE 2—Summary of Data on Clinical Course and Outcome

Case	Age at Onset	Sex	Length of Time Studied	Duration of Symptoms	Period Free from Symptoms	Outcome
1	21	M	1½ years	1½ years		Died
2	25	F	15 years	4 years	12 years	Recovered
3	24	M	12 years	2 years	10 years	Recovered
4	32	F	12 years	3 years	7 years	Recovered
5	18	M	7 years	8 months	6 years	Recovered
6	7	F	2 years	6 months	1½ years	Recovered
7	34	M	5 years	1½ years	3½ years	Recovered
8	3	M	3 months	3 months		Died
9	3	M	2 years	2 years		Under observation

and 4) for twelve years each, 1 (case 5) for seven years, 1 (case 7) for five years, 2 (cases 6 and 9) for two years each, 1 (case 1) for one and a half years and 1 (case 8) for three months. A summary of the data on the clinical course and outcome is given in table 2.

ANALYSIS OF PATHOLOGIC DATA

The pathologic changes observed at autopsy in cases of lipid nephrosis are most pronounced in the tubules of the kidney. It should be emphasized, however, that in many cases the glomeruli as well as the tubules are affected—the so-called glomerulonephrosis of Fah¹². This fact does not imply that nephrosis represents involvement of either the glomeruli or the tubules alone but rather involvement of the entire functional unit of the kidney—the nephron.

Various authors who have studied the morphologic changes in the glomeruli disagree as to whether the lesion is inflammatory or degenerative and whether or not glomerular change can be demonstrated in every case clinically typical of lipid nephrosis. The morphologic changes in the glomeruli involve if demonstrable the basement membrane, the capillary endothelial cells and the glomerular epithelial cells.

In the early stages of lipid nephrosis, it is generally agreed, there is no circulatory disturbance within the glomerular capillaries (Volhard,¹⁷ Shaw Dunn²⁰ and Bell⁹), but one must assume a functional disturbance of the capillaries, evidenced by increased permeability. This is not necessarily accompanied in the early phase by damage to the histologic structure of the glomerulus but may later lead to morphologic changes which are described as representing glomerulonephrosis. There seems to be a parallelism between the extent of the glomerular damage and the duration of the increased permeability as well as the chemical and physical nature of the protein passing through the capillary wall.

If one summarizes the glomerular changes in lipid nephrosis, two phases can be recognized: (a) an early stage, in which there is only an increased permeability of the capillaries, with no demonstrable morphologic lesion in the glomerular structure, and (b) a later stage, in which the increased permeability has produced changes in the basement membrane, the capillary endothelial cells and the epithelial cells of the glomerulus, the typical picture of so-called glomerulonephrosis. The changes observed in the cases studied here may be summarized as follows:

- 1 The involvement of the glomeruli was not uniform and was not of the same nature as the microscopic lesion observed in glomerulonephritis. A slight but not uniform thickening of the basement membrane of the capillaries was found in an occasional glomerulus. Infiltration of the glomerular cells by fatty substances was not an outstanding feature.

- 2 Changes in the tubules, especially in the proximal portion of the convoluted tubules, were the most outstanding features. There were deposits of fatty substances near the basilar portion of the epithelial cells which showed doubly refractive properties on examination with the polarizing microscope. Besides the deposit of fat or lipid material, the epithelium showed evidence of various other so-called degenerative processes, consisting of hyaline droplet infiltration and hydropic degeneration.

- 3 The lumens of the tubules were irregular and often contained an amorphous granular material, occasionally with some doubly refractive granules and a homogeneous colloid-like substance.

- 4 The interstitial tissue of the kidney did not present any inflammatory reaction.

- 5 Vascular changes in the large, medium-sized and small arteries were absent.

¹⁷ Volhard, F. in von Bergmann, G. and Staehelin, R. *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1931, vol. 6, pt. 2, p. 1046.

Dr Bell¹⁸ studied the kidney in case 8 and observed no structural change in the glomeruli. His opinion was that the appearance of the tubules supported our interpretation of lipid nephrosis.

COMMENT

The main stumbling block in the recognition of lipid nephrosis is the fact that many patients with chronic glomerulonephritis present an almost identical clinical picture. Histologically, however, the difference is easily apparent, even though there may be minimal glomerular involvement. If there is extensive tubular degeneration with scant glomerular disease, the nephrotic syndrome is likely to be most prominent clinically, on the other hand, if glomerular lesions predominate, the classic picture of glomerulonephritis prevails. Frequently there is a mixture of the two, and sometimes the nephrotic changes so dominate the picture that a diagnosis of lipid nephrosis is erroneously made.

Contrary to the opinion of some observers, the controversy concerning the identity of lipid nephrosis has not been settled but only laid aside until further investigation clears up the problem. Uncertainty and confusion still surround some of the most important aspects of the disease, particularly the nature of the glomerular changes. There is almost complete agreement regarding the lipid degeneration of the tubular epithelium, but this is not true of the malpighian tufts. Formerly the glomeruli were described as normal, but more recently Fahr,¹² Munk,¹⁹ Volhard,¹⁷ Fishberg²⁰ and others have described degenerative changes in the endothelium and epithelium corresponding to those seen in the tubular epithelium but of lesser degree. There are writers like Shaw Dunn¹⁰ who consider the changes in the glomeruli as larval forms of glomerulonephritis. Likewise, Bell⁹ has stated that the structural changes in the basement membrane of the glomerular capillaries which are revealed by a special stain represent a stage of glomerulonephritis.

After making examinations in 2 cases of lipid nephrosis with the newer special stains, Kantrowitz and Klempeier²¹ concluded that the slight swelling of the endothelial cells and the thickening of the base-

18 Bell, E. T. Personal communication to the authors.

19 Munk, F. *Pathologie und Klinik der Nephrosen, Nephritiden und Schrumpfnieren*. Einführung in die moderne klinische Nierenpathologie, ed. 2, Berlin, Urban & Schwarzenberg, 1925.

20 Fishberg, A. M. *Hypertension and Nephritis*, Philadelphia, Lea & Febiger, 1934.

21 Kantrowitz, A. R., and Klempeier, P. Ueber Lipoidnephrose, *Virchows Arch f. path. Anat.* **280**: 554, 1931.

ment membrane do not signify inflammation Hitzrot and Read²² also have presented evidence that lipoid nephrosis is a clinical and pathologic entity In these cases the clinical features of glomerulonephritis were absent, and after exhaustive histologic studies, using the staining methods advocated by Bell,²³ they found no indications of inflammatory lesions

Since the earlier studies by Munk, Volhard and Fahr,⁵ Epstein⁶ and others the problem concerning the individuality of lipoid nephrosis has been widely discussed Earlier pathologists, Aschoff, Lohlein² and Schlager,³ denied its existence Aschoff contended that a complete separation of nephrosis from nephritis is not warranted because of the histologic changes in the kidney He stated that most of the cases of nephrosis turn out to be cases of chronic glomerulonephritis Lohlein supported the idea that so-called lipoid nephrosis is the sequel to antecedent glomerulonephritis, although he had the opportunity of examining a kidney from a patient with lipoid nephrosis in which there was no conclusive evidence of preceding glomerulitis Munk,⁴ who suggested the term lipoid nephrosis, was also responsible for the theory that the changes in the kidney are secondary to a general metabolic disturbance affecting cholesterol metabolism The term nephrosis was adopted by Volhard and Fahr⁵ to include the degenerative diseases of the kidney as distinct from the inflammatory diseases Its popularity grew rapidly until it has now become well established and its position in the classification of Bright's disease is secure

In England the term has not been accepted as generally as it has in Germany and America, yet Bennett²⁴ has concluded that lipoid nephrosis exists Gamsborough⁸ said he found no justification for regarding it as a separate entity, because he saw that patients considered clinically to have lipoid nephrosis showed the features of chronic glomerulonephritis at autopsy In his opinion there is no dividing line between the two conditions, but he has concluded that the term nephrosis may be conveniently used to describe certain syndromes of nephritis In the opinion of Shaw Dunn,¹⁰ in typical cases of nephrosis the glomeruli may present only slight histologic changes It is difficult to say whether such authorities as Lohlein² and Fahr¹² would consider the glomeruli completely normal, yet it appears doubtful to many whether changes so slight and elusive can possess much pathogenic significance, especially when tubular lesions are much more pronounced After careful analysis of 9 cases Shaw Dunn concluded that nephrosis is probably a subdivision of subacute glomerulonephritis

22 Hitzrot, L. H., and Read, W. T., Jr. Clinical and Pathological Studies in a Case of Pure Lipoid Nephrosis, *Am J M Sc* **185** 233, 1933

23 Schlager. Ueber die Nephrose, *Med Klin* **14** 53, 1918

24 Bennett T. I. Nephrosis *Lancet* **1** 115, 1931

The differentiation of lipid nephrosis from chronic glomerulonephritis in this country seemed to be fairly well established until Bell²⁴ in 1929, began to cast doubt on its individuality. He was the chief sponsor of the idea that all patients with pure lipid nephrosis show some degree of glomerulitis and that the disease affects the capillaries of the glomerular tuft. This opinion is based on the fact that with special technic a decided thickening of the basement membrane of the capillaries and an increase in the number and in the size of the endothelial cells in the glomerular tuft can be found after, most likely, an initial injury to the glomerular capillaries by some toxic agent. He concluded that lipid nephrosis is to be regarded as a form of glomerulonephritis in which the glomeruli are damaged but their capillaries are only partially destroyed, so that they continue to function and tubular atrophy does not occur.

The weight of Christian's⁷ opinion caused many clinicians to accept the position that lipid nephrosis is only a stage in the course of glomerulonephritis. After a review of his large clinical experience he concluded that the term might be useful to designate a syndrome but that the condition is not a definite pathologic entity. He stated that there have been few clinical reports which show the ultimate outcome in cases of so-called lipid nephrosis.

Clinical and pathologic investigation led Blackman²⁵ also to conclude that lipid nephrosis is a form of diffuse nephritis with particular clinical and anatomic characteristics. This condition may persist for long periods, at least in children, without the development of the destructive lesions in the majority of the glomerular tufts which multiply progressively during the course of subacute and chronic glomerulonephritis. Blackman collected evidence from classic examples described in the literature and from 10 cases of his own to show that nephrosis is a particular form of diffuse nephritis in which microscopic hematuria, anemia, slight elevation of the blood pressure and a high nonprotein nitrogen content of the blood may all be found. The histologic lesions in the kidney consist chiefly of certain diffuse changes in the epithelium of the glomeruli and tubules identical with those which may occur in any form of nephritis. He emphasized that no changes in the glomerular capillaries can be recognized to account for the excretion of albumin in the urine. The most important histologic distinction between nephrosis and nephritis is the lack of coagula containing fibrin within the glomerular capsule in nephrosis. In the absence of these, clot organization and scar tissue formation, with the degeneration of the glomeruli and progressive renal insufficiency do not occur. The mechanism

25 Blackman, S. S. Jr. On the Pathogenesis of Lipoid Nephrosis and Progressive Glomerulonephritis, *Bull. Johns Hopkins Hosp.* 57:70, 1935.

responsible for this difference in the two diseases has not been fully determined. Blackman concluded that there is no evidence that lipid nephrosis is a metabolic disease.

The data for approximately 160 patients at the Mayo Clinic who presented the "nephrotic syndrome" were reviewed by Bannick.²⁶ In 30 cases a diagnosis of lipid nephrosis was justified at the time of entry. Most of the patients were followed after leaving the clinic. Seven were apparently cured, 9 described their condition as "fine," but laboratory data were not given, 4 were markedly improved but not cured, 2 were better but had glomerulonephritis, 1 showed no improvement, and 7 died, apparently with chronic glomerulonephritis. Bannick stated the belief that the insidious onset of lipid nephrosis with the high proportion of patients who have had it for years makes the clinical course different from that of ordinary nephritis and provides a basis for the theories of those who claim that it is a distinct entity. He also stated that this argument is easily met with one based on the fact that in some of these cases definite glomerulonephritis develops and the patient dies in uremia. If glomerulonephritis can be proved to have developed in 7 of 30 cases of lipid nephrosis, there must be an intimate relation between the two conditions. He concluded, however, that from the clinical standpoint there is justification for separating a group of patients with lipid nephrosis from those with ordinary nephritis in order to clarify the problem of the renal pathologic and physiologic status in general. Boyd,²⁷ too, said he regarded nephrosis as a form of glomerulonephritis in which the glomerular capillaries are damaged but not completely obscured.

It must not be thought, however, that all authorities have repudiated the concept that nephrosis is a disease distinct from glomerulonephritis. Leiter¹³ said "In its primary uncomplicated form this syndrome is known as nephrosis and is a rare disease. The rarity of the disease is no justification for the denial of its existence." He emphasized the keynote of the difficulty in differentiating nephrosis from glomerulonephritis when he said, "The nephrotic type of glomerulonephritis can mimic down to the last detail the entire clinical complex of signs and symptoms of nephrosis."

In an after-study of lipid nephrosis Major²⁸ presented 6 cases. Two of the patients died, both showing at autopsy marked evidences of chronic glomerulonephritis. Three apparently made a complete

26 Bannick, E. G. Lipoid Nephrosis and Its Relation to Glomerular Nephritis, *J. A. M. A.* **102** 172 (Jan 20) 1934.

27 Boyd, W. The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1932, p. 437.

28 Major, R. H. After-History of Lipoid Nephrosis, *Am. J. M. Sc.* **191** 46, 1936.

recovery and were observed over a long enough period to substantiate the clinical diagnosis

From the clinical standpoint Stone²⁹ said he believed there is ample reason to retain the identity of this little known lipid form of Bright's disease, since it is distinguished from other main types by certain particular features. Stone stated that about 20 per cent of the patients with lipid nephrosis may recover after a period of invalidism lasting from a few months to a year or more. In about 20 per cent death will occur from exhaustion or malnutrition, and 50 to 60 per cent will die from terminal streptococcic or pneumococcic peritonitis. After a comparison of Stone's experience with our own it appears that the prognosis was much better in our series.

• Shapiro³⁰ has emphasized his belief that pure lipid nephrosis does exist and has cited a case in which there was no evidence of glomerulonephritis. He said he believed that even if some glomerular changes, such as swelling of the epithelium of Bowman's capsule and lipid degeneration of the glomerular tufts, are noted, a degenerative rather than an inflammatory process is signified and, furthermore, that the finding of an occasional glomerulus showing a definite inflammatory reaction does not constitute the picture of glomerulonephritis.

Five patients presenting the clinical signs of the nephrotic syndrome were reported on by Landis and Elsom³¹. By using the Addis method they pointed out that 3 showed no clinical signs of glomerulonephritis and excreted from 200,000 to 800,000 erythrocytes in twelve hours and 2, with clinical signs of subacute glomerulonephritis, excreted 4,000,000 erythrocytes in twelve hours.

After studying various forms of nephritis Terbruggen³² concluded that lipid nephrosis exists as a disease entity. He reported the case of a boy aged $2\frac{1}{2}$ years who died of pneumococcic peritonitis. At autopsy the glomeruli showed no adhesions of the capillaries, and the endothelial cells in only a few loops were swollen. Particular attention was paid to the basement membrane of the capillaries, but widening and swelling could not be demonstrated with ordinary or special azo stains. There were no morphologic changes that were typical of glomerulonephritis. He said he did not believe that there is a primary glomerulonephritis but that a toxin increases the permeability of the glomerular capillaries.

29 Stone, W. J. *Bright's Disease and Arterial Hypertension*, Philadelphia, W. B. Saunders Company, 1936.

30 Shapiro, P. F. *Lipoid Nephrosis. Pathology, Genesis and Relation to Amyloidosis*, *Arch. Int. Med.* **46** 137 (July) 1930.

31 Landis, E. M., and Elsom, K. A. *The Nephrotic Syndrome in Adults*, *Internat. Clin.* **1** 1, 1937.

32 Terbruggen, A. *Degeneration, Speicherung und Nephrose*, *Klin. Wchnschr.* **14** 1305 and 1345, 1935.

In the opinion of Matthew and Cameron the primary renal change in lipid nephrosis is the increased permeability of the capillary membrane which allows substances of unusually large molecular content to escape from the blood. They suggested, too, that nephrosis is merely syphilis of the kidney.

Elias³¹ said he recognized the existence of lipid nephrosis anatomically. He concluded that it is due to some chronic infectious disease such as syphilis, malaria or tuberculosis.

Among the recent publications of great importance on the subject of lipid nephrosis is the article by Randerath.¹¹ He observed that the glomerular epithelial cells show cloudy swelling or hyaline degeneration in addition to thickening of the basement membrane of the capillaries. Various loops of the glomeruli are affected in later stages, and widening and swelling of the capillary wall of the glomeruli and the parietal covering of the capsule are seen. There may also be hyaline clumping of the glomerular loops. In summarizing, Randerath said that the primary change in lipid nephrosis is increased permeability of the glomerular capillaries, occurring with or without demonstrable damage to the capillary wall and leading to secondary changes in the tubular epithelium and glomeruli.

A recent review of the question of lipid nephrosis by Fahr¹² is also interesting. He has emphasized again that true lipid nephrosis is fundamentally different from glomerulonephritis and that although there is difficulty in differentiating between the two conditions, the belief that they are distinct is growing. The lesions in the glomeruli are not inflammatory and are best described as indicative of "chronic glomerulonephrosis."

Analysis of our 9 cases has led us to believe that lipid nephrosis is fundamentally different from glomerulonephritis and that patients in whom nephritic symptoms develop never have had true nephrosis. Histologic examination in 2 cases showed the characteristic features of lipid nephrosis. There were no evidences of inflammation in the glomeruli, but degenerative changes were seen in the endothelial and epithelial cells of the tuft. Obviously we were unable to determine whether or not thickening of the basement membrane might develop later as emphasized by Fahr.³⁵

We agree with those authorities who say that nephrosis is often simulated by chronic glomerulonephritis but that the primary form of the disease is seldom seen. The lack of autopsy material, however, has

33 Matthew, E, and Cameron, J. D. S. Chronic Nephrosis, Edinburgh M. J. **40** 569, 1933.

34 Elias, H. Ueber Nephrosen, Wien klin. Wchnsch. **48** 1177, 1935.

35 Fahr, G. What Is Lipemic Nephrosis? Am. J. M. Sc. **194** 449, 1937.

given an exaggerated view of its rarity because most patients recover. We have concluded that the slight changes occurring in the glomeruli are not inflammatory and do not indicate glomerulonephritis. Notwithstanding the differences of opinion regarding the significance of the minimal lesions, the fundamental fact remains that patients with such renal changes show a very different course from those with true glomerulonephritis. In spite of all the arguments advanced by those who have given this controversy careful consideration, we believe that the distinctive course and the favorable prognosis are sufficient grounds for retaining the term nephrosis in the classification of Bright's disease.

SUMMARY

A factor of fundamental importance in the clinical study of any form of Bright's disease is the length of time the patient has been observed. Lipoid nephrosis, more than any other form of Bright's disease emphasizes that a long, detailed study and proper evaluation of signs and symptoms are necessary for an accurate diagnosis.

Our purpose in reporting this series of cases is (*a*) to show by histologic and prolonged clinical study that lipoid nephrosis is different from chronic glomerulonephritis with the nephrotic syndrome and that there is justification on clinical grounds alone for this distinction, (*b*) to establish lipoid nephrosis as a clinical and pathologic entity, in order to arouse further investigation into the cause of the hyperpermeability of the glomeruli for protein, the production of edema and the abnormal metabolism of cholesterol in these cases, (*c*) to show the practical importance of the fact that patients with lipoid nephrosis recover while those with chronic glomerulonephritis usually do not, and (*d*) to present a clinical study with prolonged observations and histologic examinations which may help to clarify some aspects of the controversy and may help to establish the individuality of lipoid nephrosis.

In this report 9 cases of genuine lipoid nephrosis are presented and discussed. Two patients died and were studied post mortem, 6 recovered completely and 1 is under observation. The period of study of these patients varied from three months to fifteen years. Most patients were observed longer than seven years.

The histologic examination of the kidneys of the 2 patients studied post mortem failed to show evidences of chronic glomerulonephritis. Degenerative changes characteristically described as features of lipoid nephrosis were present. In 1 case the special staining methods of Bell were used, and not even thickening of the basement membrane of the capillaries was observed.

A review of the theories of many of the prominent clinicians and pathologists who have made a study of lipoid nephrosis is given. It is

pointed out that the fundamental change in lipoid nephrosis is the hyperpermeability of the capillaries of the glomeruli. This functional disorder is associated with profound albuminuria followed by generalized edema. Whether or not this functional derangement is followed by a structural alteration is a problem to be determined in the future. A satisfactory explanation is lacking for this hyperpermeability.

This report tends to support the view that there is justification for the distinction between lipoid nephrosis and chronic glomerulonephritis. We believe that there are ample grounds for this because of the favorable prognosis in lipoid nephrosis as contrasted with the poor one in chronic nephritis. We conclude from our clinical and pathologic studies that although lipoid nephrosis is a rare disease compared with chronic nephritis, there is sufficient reason for maintaining the distinction of lipoid nephrosis in the classification of Bright's disease.

THROMBO-ENDOCARDITIS IN RABBITS

A NEW DISEASE DUE TO AN INTRAVIRUS (?)

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During the last five years, by means of numerous experiments which have been reported separately in Italian reviews,¹ we have fully described from the anatomic, bacteriologic, macroscopic and microscopic stand-points a new disease that can be caused in rabbits by several experimental procedures

We shall here summarize briefly what we have observed and deduced from our experiments as to the nature and genesis of this new disease. The starting point of our experiments was an attempt to transmit the infection which is the cause of rheumatic fever in man to young rabbits by injecting blood from infected persons. We noted that an endoperitoneal injection of 5 to 10 cc of infected blood, freshly taken from the vein and unchanged by the addition of anticoagulant agents, frequently caused in the rabbit a morbid process, consisting essentially of thrombo-endocarditis, the morphologic features of which will be described later.

We obtained the same result, although less frequently, by using blood from nonrheumatic persons, and this made us doubt the possibility of having transmitted the rheumatic infection from man to animal. As a matter of fact, subsequent experiments showed that the blood of

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1. Andrei, G. and Ravenna, P. (a) Experimental Researches on the Etiology and on the Pathogenesis of Rheumatic Fever, *Acta rheumatol* **6** 12 (Dec.) 1934, (b) Ricerche sperimentali sulla eziologia e sulla patogenesi del reumatismo articolare acuto, *Riv di idroclimat, talassol e terap fis* **46** 166 (April) 1935, (c) Ricerche sulle infezioni focali. La questione del tropismo elettivo degli streptococchi, *Boll d Ist sieroterap milanese* **13** 229 (April) 1934, (d) Ricerche sulle infezioni focali. La produzione sperimentale di lesioni simili a quelle del reumatismo articolare acuto, *ibid* **13** 804 (Oct.) 1934, (e) Ulteriori ricerche sull'eziopatogenesi del reumatismo acuto e dell'endocardite sperimentale del coniglio, *ibid* **14** 713 (Aug.) 1935, (f) Sulla natura ed il significato della tromboendocardite sperimentale del coniglio *ibid* **16** 138 (March) 1937

healthy rabbits, normal and sterile horse serum and unskimmed and sterilized milk also, when used in the same manner, are likely to cause the disease in a number of cases

TECHNIC

From 15 to 30 cc of blood was drawn directly from the bend of the elbow and immediately injected with the same syringe into the peritoneal cavity of three or four rabbits in doses of from 5 to 6 cc for each animal, without the use of any anticoagulant agent. When blood is quickly withdrawn and injected there is no time for it to coagulate. If rabbit blood in about the same amounts is obtained from the heart and injected directly, it is advisable to draw the blood in a syringe containing a small quantity of sodium citrate, as otherwise coagulation will occur quickly.

The horse serum used was the usual commercial serum contained in sterile ampules for injection, the dosage was practically the same as that used in the case of whole blood.

The blood filtrate was obtained by a special procedure, as we wished to filter the whole blood, not just the serum and the plasma, which, as is well known, are generally less rich in bacteria than is whole blood. Also the plasma obtained by strong centrifugation may be poorer in bacteria than is whole blood.

As far as is known, a total blood filtrate cannot be obtained, because the red blood cells obstruct the pores of the filter, neither can hemolyzed blood be filtered, since the stroma will act in the same manner. Therefore, to the blood rendered noncoagulable by the addition of 2 cc of a 15 per cent solution of sodium citrate for each 20 cc of blood, an equal amount of sterile physiologic solution of sodium chloride was added. Centrifugation at low speed was carried out for a few minutes in order to precipitate most of the red blood cells but not the white blood cells. Then the supernatant fluid, which was still rather thick, was collected and filtered through an L₂ Chamberland filter. By repeating the same procedure several times we thought that we obtained the hypothetical virus of the blood in the resulting fluid. The blood was filtered with Martin's apparatus, a suction of not over 60 cm of mercury being used. The efficiency of the procedure was continually controlled by the addition of *Bacillus prodigiosus* according to the usual bacteriologic technic, for in this manner the filtering of the fluid is accomplished more quickly. The filtrate obtained from 5 cc of blood was injected into each rabbit, and two rabbits received injections at the same time of the same material.

For another series of experiments we made use of a suspension of endocarditic vegetations. To obtain the suspension we proceeded as follows. With a perfectly sterile technic, the thorax of the animal was opened as soon as it had been killed. The heart was removed and placed in a Petri dish. Then it was opened, and so far as possible contact with air was avoided. If endocarditic lesions were found, the valves and the thrombotic vegetations were removed, immediately triturated in a sterile mortar and suspended in a small quantity of sterile physiologic solution of sodium chloride, to be injected into the peritoneal cavity.

For our experiments we always made use of young rabbits, aged 30 or 45 days, but we wonder whether such a condition was essential. However, this was the starting point of our experiments, since we thought that young animals, which had never been used previously by other investigators, should be more sensitive to the hypothetical virus in question. Since we obtained positive results with young rabbits, we did not think it advisable to use old rabbits also, instead, we tried to work out more important details.

As will be shown later, positive results were obtained with a number of animals which had each received an injection about three weeks before, lesions of endocarditis were observed only exceptionally before this time. Nevertheless, we waited usually four to six weeks before killing the animals, since in this manner gross lesions were obtained.

Through transmission serially we obtained positive results using the blood and the endocarditic vegetations removed from animals which had been inoculated one or two months previously. The animals that had received injections were isolated with great care in eight different compartments. We did not think it a sufficient guaranty of isolation to put them in different cages, although many iron cages were at our disposal which could have been perfectly sterilized.

ANATOMIC DESCRIPTION

The most important form of the disease was thrombo-endocarditis usually clearly evident although of varying intensity, affecting the right side of the heart, especially the tricuspid valve, and sometimes the walls of the ventricle and of the auricle, the tendinous cords and the papillary muscles. Lesions of the left ventricle were rare, and only the mitral valve and its tendinous cords were ever involved. The most important lesion consisted of verrucous, gray, reddish gray or rose-colored thrombi which adhered tenaciously to the underlying tissue and were friable.

Macroscopically, the valves did not show any alteration other than an occasional gelatinous aspect, more usually of the mitral valve. Microscopically, the thrombi looked like white thrombi, having a stratified structure like that of a sand bed, which sometimes alternated with a layer of red thrombi. The substance forming them had either a fine reticular or homogeneous appearance, it stained well with eosin, it did not always respond to Weigert's test for fibrin and it usually contained a small number of white blood cells, mostly lymphocytes or polymorphonuclear pseudo-eosinophils.

The microscopic changes in the valves were rather scanty, more often than not the valve was thinner without an endocardium in the part where the thrombus adhered, while at other times it was thick, with an edematous appearance.

The classic features of inflammation were nearly always absent, since, as is now well known, exudation of serum is considered by modern pathologists as the chief or the only evidence of inflammation.

Sometimes we noted slight hyperplasia of the valvular tissue, with some formation of blood vessels and with a considerable proliferation of the endocardium so as to form a vegetation on the valves, which was seen at a glance to be granular. In one of the few cases in which we kept the animal alive many months after the injection we observed sclerosis affecting the mitral valve and a tendinous cord extending down to the corresponding papillary muscle the newly formed connective

tissue still had the features of young tissue and showed considerable parvicellular infiltration

The myocardium often remained exempt from lesions, and only in a few cases did we observe small nodular or diffuse infiltrations, constituted nearly always of elements of a lymphocytic type and of some polymorphonuclears, although epithelioid and plasma cells and rare giant cells sometimes were present. The muscular fibers when the infiltrations were small were only dissociated, but if the nodules were large



Fig 1—Endocarditic lesions (right ventricle) resulting from the injection of blood from a patient with rheumatic fever. The rabbit was killed sixty-three days after the intraperitoneal injection of 5 cc of blood

they also showed regressive changes which might reach hyaline degeneration and necrosis. However, we noted substantially similar lesions also in the myocardium of rabbits which had undergone different treatment, for instance, those which had been given injections of streptococcus cultures in the course of the experiments on focal infections¹. Therefore, we do not think that these lesions stand in strict relation to the endocarditic lesions considering the rarity and lack of parallelism

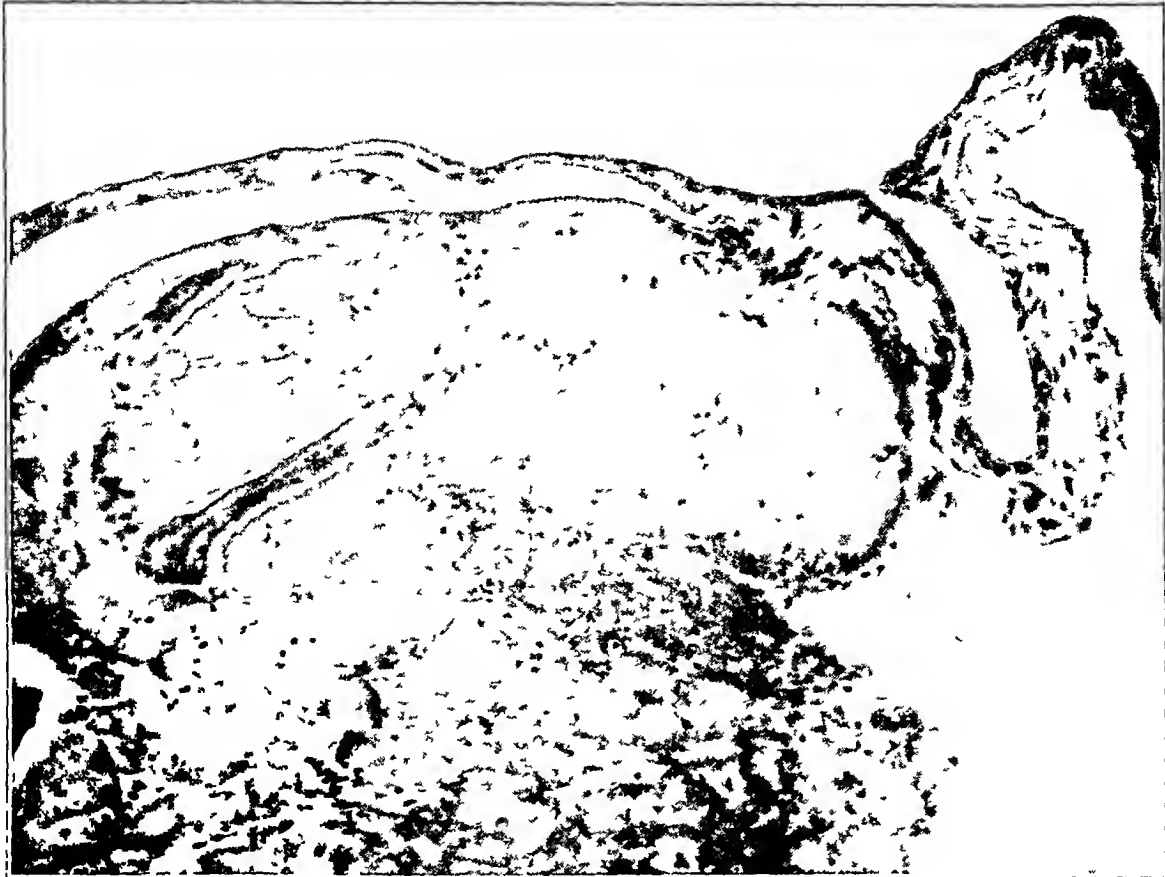


Fig 2—Slightly enlarged photomicrograph of a section of a large thrombus on the tricuspid valve of a rabbit killed forty-four days after the injection of blood from an endocarditic rabbit. Note the scantiness of the cellular elements contained in the thrombus and the thinness of the part where the thrombus adheres. Hematoxylin stain.



Fig 3—Slightly enlarged photomicrograph of the insertion of a tendinous cord into the edge of the tricuspid valve of a rabbit which died twenty-three days after the injection of blood from an endocarditic rabbit. Note the hypertrophy and hyperplasia of the connective tissue and the great proliferation of the endocardium, which has formed granular elements, visible at a glance, on the surface of the valve. Hematoxylin stain.

between the degree of development of the two kinds of lesions and the fact that similar lesions have been observed with great frequency by Miller in cases of spontaneous disease

The macroscopic and microscopic lesions were always and exclusively confined to the heart, we never found any lesions in the other viscera except lesions of coccidiosis, the presence of which had no relation to the cardiac lesions. The articulations were not involved except for thickening of the reticulohistiocytic layer of the synovial membrane similar to that occurring in rheumatic arthritis of man and sometimes also in nonendocarditic animals, being without specific character

BACTERIOLOGIC EXAMINATION

All samples of material injected (e. g. blood, milk and serum) were constantly found sterile when placed in common mediums

The bacteriologic examination of the heart, circulating blood, principal viscera (liver, kidney and spleen) and articulations of animals affected with endocarditis constantly gave negative results

Our macroscopic and microscopic anatomic description and our bacteriologic results have been fully confirmed by the control researches that Chini has recently published

PATHOGENESIS OF THROMBO-ENDOCARDITIS

From the morphologic and bacteriologic features mentioned it appears that we are dealing with a disease that has not yet been described as present in rabbits, either as a spontaneous disease or as one caused by means different from the ones which are likely to produce it through a well known and essentially bacterial action. Although spontaneous endocarditis has never been observed in rabbits, as stated also in Jaffe's recent treatise, it was necessary to ascertain whether our rabbits might not be an exception. Therefore since in live rabbits it is impossible to detect the existence of endocarditis, which is not revealed even by alterations of nutrition or by diminution of growth, we examined many control animals. For each series of experiments some of the animals from the same breeding farm were employed in the researches, while others, which had undergone no treatment, were examined at once or after a certain lapse of time

Of this group of controls, 180 were examined, some were examined on their arrival from the breeding farm but most of them after a few months' stay in compartments in which no case of endocarditis had yet appeared, so that they could be considered as not yet infected

2 Jaffe, R. Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumstiere (Kaninchen, Meerschweinchen, Ratte, Maus), Berlin Julius Springer, 1931

Endocarditis was found in only 4 animals, strictly speaking, in 2 cases it should be considered as spontaneous, the other 2 animals were kept for several months in cages that, having been occupied by a number of endocarditic rabbits, could be considered infected, as will be seen from what will be stated later. It follows therefore that endocarditis in the animals we used appeared spontaneously only with extreme rarity.

The same conclusion may be deduced from some other observations. Of 263 rabbits which had undergone the various procedures likely to cause endocarditis and which had died within three weeks after the injection, only 3 showed endocarditic lesions, while of the 441 that lived longer, as many as 163 were endocarditic. This fact, besides having the aforementioned meaning, has enabled us to infer that the time necessary for the appearance of endocarditis exceeds three weeks after the injection.

Lately Chini, one of those who have undertaken the control study of our results, has advanced the suggestion that the incubation time may be even shorter, about four to eight days. We cannot exclude the fact that this may happen also if some conditions affecting the rabbits and the virulence of the hypothetical virus are varied, but in this case these facts, as well as the attempts at transmission, have not yet been demonstrated, since, owing to the particular conditions under which Chini's experiments were made, it is possible that the animals in which endocarditis was noted after a few days were spontaneously affected with the same disease even before the injection was given. Most of the rabbits came from a small breeding place where, as Chini himself demonstrated, the disease occurred spontaneously with great frequency.

Owing to the modalities of the provoking treatments which we carried out, chiefly the injection of sterilized milk, we could reject the hypothesis that the disease in rabbits is to be ascribed to a pathogenic agent contained in the injected material. Therefore only two hypotheses were left for consideration in interpreting the observed facts: (1) that endocarditis might be ascribed to infectious agents preexisting in the animal and activated by the experimental treatment and (2) that the disease might be ascribed directly to the chemical or chemicophysical action of the injected material.

A physical or chemicophysical etiology appeared hardly probable at first sight, because nothing similar has ever been ascertained after such treatments by hundreds of careful research workers, so it was logical to consider the influence of some other factor which perhaps was not common to all the rabbits. Therefore, subsequent researches were made so as to bring into evidence the infectious nature of the disease, which seemed the most probable factor.

In view of this hypothesis the most complete isolation was maintained for the development of further researches, as has been stated in the description of our technical procedure

The first experiments consisted of injecting whole blood and blood of endocarditic rabbits filtered through an L₃ Chamberland filter, and these yielded widely positive results. Seventy-two of the 118 rabbits were affected with endocarditis (we include here and later only animals which either died or were killed more than three weeks after the injection). However, this type of experiment has no absolute meaning,

TABLE 1—*Summary of Data**

Injected Material	Rabbits Which Died More Than 3 Weeks After Injection		Rabbits Which Died Within 3 Weeks After Injection	
	Total No of Rabbits	No of Endo carditic Rabbits	Total No of Rabbits	No of Endo carditic Rabbits
Blood from patients with rheumatic fever	105	43	35	3
Blood from patients not affected with rheumatic fever	115	21	28	0
Blood from healthy men	5	0	12	0
Blood from endocarditic rabbits	90	54	44	0
Blood filtrate from endocarditic rabbits	28	18	12	0
Blood from healthy rabbits	18	2	16	0
Suspension of endocarditic vegetations	10	4	8	0
Normal sterile horse serum	18	5	22	0
Sterilized unskimmed milk	52	16	28	0
<i>Streptococcus</i> cultures (injected intravenously)			58	0†
Totals	441	163	263	3

* Of 180 rabbits which received no treatment, 4 appeared to be affected with endocarditis. It should be noted that 2 of these 4 rabbits had been kept a long time (several months) in a compartment that was supposed to be infected.

† The 6 rabbits with polypous endocarditis observed in this group of animals are not mentioned here, because their condition was entirely different from the endocarditis in question. For the description of the morphologic picture reference should be made to our work entitled "La questione del tropismo elettivo degli streptococchi" 1c

because the result may be ascribed, in the absence of a virus in the injected material, to the mechanism set in action by the injection of sterile milk. In order to avoid this objection, we attempted to transmit the disease by means of small quantities of material rich in virus, such as the endocarditic vegetations. Four of 10 rabbits showed evident endocarditis after injection into the peritoneal cavity of a suspension in physiologic solution of sodium chloride of the vegetations from two hearts, removed by a perfectly sterile process.

A subsequent series of experiments was carried out in order to ascertain whether the disease, once induced, could be transmitted spontaneously to other animals. We were led to this attempt also by the observation of a few cases of endocarditis in rabbits that had been

kept a long time in compartments and cages in which endocarditic rabbits had previously been kept. For this purpose we inoculated some rabbits with either human blood or milk, then we immediately put 2 inoculated and 2 noninoculated rabbits in each cage. In this manner, allowing for a three week incubation period for the disease after the inoculation, allowing several days for the hypothetical spontaneous spread of the disease from the infected rabbits to the others living in the same cages and estimating the time necessary for the disease to develop in the latter animals as twenty-one days, we could foresee that theoretically the infection could not be manifested until fifty days or more after the experiment was started. In fact, of 19 animals which had not been given injections but which had been kept in a cage with endocarditic rabbits for not less than fifty days, as many as 8 were affected with grave thrombo-endocarditis, while of the 16 that had lived for a shorter

TABLE 2—*Attempts to Transmit Endocarditis Spontaneously*

	Total No of Rabbits	Endo- carditic Animals
Rabbits which had remained more than 50 days in a cage with endocarditic animals	19	8
Rabbits which had remained less than 50 days in a cage with endocarditic rabbits	16	0

time, none seemed to be diseased. At the same time some other rabbits, although they had been given injections, did not appear to be affected later with endocarditis, and none of several rabbits living in common with them seemed to be diseased.

In this manner we obtained evidence that one of the following conditions is necessary for the appearance of endocarditis: (1) the injection of specified material (for instance, human or rabbit blood, horse serum, milk or suspension of endocarditic vegetations) or (2) prolonged contact with other rabbits affected with endocarditis. The conditions of life, feeding and other features common to all animals had no influence on the appearance of endocarditis.

CONCLUSIONS

On the whole, the described experiments permit the following conclusions:

It is possible to cause a disease not previously described in rabbits—thrombo-endocarditis—which shows rather characteristic clinical and anatomic features.

The means likely to cause the disease consist of an endoperitoneal injection of human or rabbit blood, horse serum or sterile milk. We

have not excluded the possibility that a procedure differing from ours as to manner of introduction or as to the nature of the injected material may not produce the same result. For five years this phenomenon was constantly obtained with remarkable frequency in a number of rabbits coming from different breeding places in the province of Turin.

That an infectious disease was present was demonstrated by the transmission by injection of a minimal quantity of material (suspension of endocarditic vegetations), rather than by anatomic characteristics, and mostly by the evidence of spontaneous infection from one animal to another.

The constant sterility of the blood and viscera of the affected animals enabled us to ascribe the disease to an unknown virus, probably an *infravirus*. The latter must have been latent in the animals, because the disease was caused also by the injection of sterile material, which evidently made the animals sensitive to the pathogenic action of the virus or directly increased the virulence of the virus.

In our animals the disease was almost always directly dependent on the treatment given, since the occurrence of spontaneous endocarditis was demonstrated as being exceptionally rare in our animals.

It is, however, possible that in other cases the disease may appear spontaneously with greater diffusion when the animals contain a more active virus or are more sensitive to it, which means that in nature conditions might be realized which in our animals were brought into action with technical artifices. This has lately been demonstrated by Chini, who, in studying a large number of animals for several years with negative results, has observed that there is a small breeding place where endocarditis is spontaneous and frequent.

The whole problem reminds us of the problem centered about Miller's number 3 virus. As is well known, this virus was made evident by the injection of blood from persons affected with rheumatic fever into the testicle of a rabbit and by successive rapid transmission from one animal to another, always by way of the testicle, until the appearance of the characteristic orchitis. But in our cases the localization and the character of the lesions, the conditions of transmissibility which revealed the persistence of the virus in each animal for a longer time and the existence of a longer period of incubation demonstrated definitely that Miller's virus was not concerned.

The disease we have described presents a twofold interest. First, the possibility of its appearance after various experimental treatments should be borne in mind by any one undertaking further study of the transmission of infectious diseases, as it may constitute a source of error, especially on account of its anatomic similarity to the lesion of human rheumatic endocarditis, and, secondly, this disease constitutes

a new example of the phenomena of biotropism the study of which, just begun in experiment animals, will probably reveal unhoped for applications to human pathologic conditions

SUMMARY

We have described a new disease of rabbits, thrombo-endocarditis, which, although occasionally spontaneous, may frequently be caused by various forms of treatment, which may be transmitted from one animal to another either by means of small quantities of infectious material or spontaneously, and which has been ascribed to a virus which is still unknown and is probably infaivisible

PNEUMOCOCCIC ENDOCARDITIS

JAMES M RUEGSEGGER, M D

CINCINNATI

Pneumococcic endocarditis is considered a relatively rare condition, although a review of the literature discloses numerous case reports of the disease Osler,¹ Netter,² Preble,³ Menetrier,⁴ Locke⁵ and Thayer⁶ have reported on series of personally observed patients or on collected reports of cases In 1927 Goldstein and Goldstein⁷ reported 8 cases of pneumococcic infection in which endocarditis was noted post mortem, although the cause of the endocarditis remained in doubt in several instances Subsequently, other authors⁸ have reported isolated cases or small groups of cases of pneumococcic endocarditis, the diagnosis having been made by inference, by bacteriologic methods or by histologic study of the vegetation

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Dr Ralph Johansmann, of the Department of Pathology, cooperated in this study

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The present report is based on a study of 19 patients with pneumococcic endocarditis, 17 of whom were observed by me. While the presentation deals largely with the incidence, predisposing factors, clinical data, methods of treatment and necropsy observations, an attempt is also made to set up bacteriologic and clinical criteria for the prompt diagnosis as well as the treatment of this disease.

The inference should be that acute endocarditis occurring during the course of lobar pneumonia should be considered pneumococcic in origin until proved otherwise. Preble³ found less than 6 per cent of exceptions to this dictum. On the other hand, Locke⁵ found that more than 50 per cent of the cases of acute endocarditis occurring during pneumonia were due to organisms other than the pneumococcus. With improved methods of culture and rapid identification of the pneumococcus, it is believed that these discrepancies will largely disappear. Locke's dogmatic statement, "The final test should always be the actual demonstration of the pneumococcus in the valves," not only is almost impossible of fulfilment but precludes the making of the diagnosis ante mortem. Moreover, the identification of pneumococci in the vegetations must rest on bacteriologic rather than on morphologic evidence. In 10 of the 15 cases in which autopsy was performed, the vegetations were cultured, each time the same pneumococcus was grown which was cultivated from the blood of the patient during life. Lord pointed out the danger of contamination from the blood of bacteremic patients. In addition, the following method was employed, which at least partially obviates the possibility of blood contamination. The heart is preserved in solution of formaldehyde as usual, after varying intervals, portions of the vegetations are removed, washed thoroughly in sterile saline solution, macerated and inoculated into blood broth. This method has yielded pure cultures of pneumococci in vegetations which had remained in preserving solutions as long as twenty-two months, in each instance the pneumococcus was of the same type as that detected in the body during life. This finding is certainly more than a coincidence and lends support to the belief that acute endocarditis occurring during the course of pneumococcic pneumonia with bacteremia is due to the pneumococcus rather than to some other organism. As further evidence that these endocarditides are due to the pneumococcus, gram-positive lanceolate diplococci were demonstrated in the vegetations histologically.

In view of the fact that there are potent serums available against several types of pneumococci, it seems timely to set forth certain criteria which enable the diagnosis to be made and treatment to be instituted. The persistent presence or the recurrence of pneumococcemia is presumptive evidence of a purulent focus and is indispensable in substantiating the diagnosis of endocarditis. This alone, however, is not sufficient. Embolic phenomena occurring in patients with pneumo-

coccemia are strongly presumptive evidence of endocardial damage. The appearance of signs of valvular incompetence during diastole in the presence of bacteremia may be safely referred to endocarditis (Pieble). Thayer also said he considered such signs as confirmatory. Systolic murmurs must be evaluated much more carefully, for obvious reasons, the sudden appearance and persistence of such a murmur should, however, arouse suspicion of organic change. These signs may not be present in every case, in fact, the application of these criteria permitted diagnosis of endocarditis in only 10 of the 19 cases reported. Nevertheless, such criteria did not lead to a mistaken diagnosis in a single instance.

During the twenty-three month period from Oct. 1, 1935, to Sept. 1, 1937, 655 patients were admitted to the medical service of the Cincinnati General Hospital with acute pneumococcal infection. The latter term is used in preference to pneumonia, for in a few instances it was impossible to ascertain whether the endocarditis had preceded or whether it had been a sequel of pneumonia, in others, bacteremia was known to have existed longer than the necropsy indicated the pneumonic lesions had been present. In this series of 655 patients the diagnosis of acute endocarditis was made in 19 instances, either clinically or by pathologic and bacteriologic methods. Thus in this series the incidence of endocarditis in acute pneumococcal infection was 2.9 per cent. In the literature the incidence has been reported as varying from 0.06 to 2 per cent. In 104 of the 214 fatal cases necropsy was performed, and in 15 cases (14.6 per cent) acute endocarditis was observed. This incidence is much higher than that recorded by any author except Osler,¹ who reported 16 in 103 necropsies. Wherever clinical and necropsy incidences are recorded, there is a great discrepancy in the figures, as noted in the present series, and the impression cannot be escaped that pneumococcal endocarditis is considerably more common than is usually supposed.

A consideration of the relative frequency of the etiologic agents of bacterial endocarditis tends also to show that the importance of the pneumococcus may have been underestimated. During the same twenty-three month period 46 necropsies revealed acute or subacute vegetations on one or more valves, and in 15 cases the vegetations were proved to be due to the pneumococcus. There was an additional instance of acute vegetative endocarditis, the patient dying of purulent meningitis (gram-positive diplococci) and empyema, but it is not included in this series because no bacteriologic studies were made.

PREDISPOSING FACTORS

Sex does not appear to have any importance as a predisposing cause. In this series there were 14 males (73.8 per cent) and 5 females (26.2

per cent) This ratio prevailed almost exactly for the whole group of patients with acute pneumococcic infection, the figures being 72.3 and 27.7 per cent, respectively

Likewise, race does not seem to be a factor Fifty per cent of the cases of acute pneumococcic infection occurred in the Negro race, and the mortality percentage of white and Negro patients did not vary appreciably Ten of this series of patients with endocarditis were white, and 9 were Negroes

Pneumococcic endocarditis may occur at any age It is, however, primarily a disease of middle and later adult life Whereas more than half the patients with acute pneumococcic infection were of the age group from 11 to 40, patients under 13 not being admitted to the medical service, 80 per cent of the patients with endocarditis were over 40 However, patients in the fifth and sixth decades comprised a preponderance of the series This is in marked contrast to subacute bacterial endocarditis, which shows a predilection for the younger age groups

The apparent increase in the incidence of this complication may raise the question of serum therapy as a predisposing cause Eight of the infections were caused by types of pneumococci for which therapeutic serum was not available In only 5 of the remaining 11 cases was serum given Consequently, it is doubtful if serum therapy is a predisposing factor in the causation of this disease

Since Wadsworth⁹ first called attention to the occurrence of pneumococcic endocarditis in horses, the opinion has been expressed that the type I pneumococcus was chiefly concerned in producing this complication In this series several types of organisms occurred relatively more frequently than type I pneumococcus (table 1) This is in accord with the findings of Finland and his associates¹⁰ who found pneumococci of type II and type V to be the more frequent, relatively and absolutely, in a large series of necropsies Since Bullowa and Wilcox¹¹ have shown that pneumococci of type II, type III and type V of the commoner types are more likely to invade the blood stream than those of type I, it seems unreasonable to adhere to the belief that those of type I are primarily responsible for the production of endocarditis, especially in view of clinical evidence to the contrary

Preexisting disease of the valvular endocardium apparently has little influence as a predetermining factor in pneumococcic endocarditis In

9 Wadsworth, A. B. A Study of the Endocardial Lesions Developing During Infections in Horses, *J. M. Research* **39** 279, 1918

10 Finland, M., Brown, J. W., and Ruegsegger, J. M. Anatomic and Bacteriologic Findings in Infections with Specific Types of Pneumococci, Including Types I to XXXII, *Arch. Path.* **23** 801 (June) 1937

11 Bullowa, J. G. M., and Wilcox, C. Incidence of Bacteremia in the Pneumonias and Its Relation to Mortality, *Arch. Int. Med.* **55** 558 (April) 1935

this entire series of 19 patients, valvular incompetence due to an antecedent infection was diagnosed only once, although 2 other patients had a history of rheumatic symptoms. Four of the patients had serologic evidence of syphilis, but none had signs of syphilitic aortitis or valvulitis.

As a rule the portal of entry of the pneumococcus is reasonably clear. In 15 of the cases the endocarditis followed frank lobar pneumonia while the patient was under observation, or there was a history typical of that disease. Case 4 probably represented a case of invasion from the urethra, although cultures were not made previous to the onset. Bacteremia developed in case 9 after cholecystogastrostomy for obstruction of the common duct. In 1 patient (case 11) fever developed suddenly while he was staying in the hospital to regain cardiac compensation, and he died three days later. In another case (case 3) the onset was insidious, the only complaint being of a sore knee, which represented a purulent metastatic focus of the infecting organism.

CLINICAL COURSE

Pneumococcic endocarditis may complicate pneumonia at any stage of the illness or may occur independent of the disease days or weeks after an apparently uneventful convalescence. If the endocarditis merges with the acute pulmonary infection in regard to time of appearance, it is likely not to be diagnosed. As a rule the onset is rather acute. Six of the patients were afebrile for from two to seven days, when the complication was heralded by a sudden chill with subsequent fever. All but 3 (84 per cent) of this group of patients had chills or chilly sensations, separate and distinct from such symptoms occurring in the early stages of lobar pneumonia, during the course of illness that were directly referable to the endocarditis. The fever was sustained in 12 of the 19 cases, the temperature ranged between 103 and 105 F (rectal). Four patients showed an intermittent type of fever, although the afebrile periods were of short duration. Three patients had paroxysms of fever with chills, the maximum temperature reaching 108 F. One patient, observed for only three days, was afebrile during the first two days. In only 1 case was the fever moderate, the temperature being sustained between 101 and 102 F.

The pulse rate was invariably accelerated. However, the instability as to rate and volume rather than the actual rate was the outstanding characteristic of the pulse.

As a rule evidence of toxemia was marked. This was especially striking since there were not always signs localizing the infection.

Acute pneumococcic infections of the endocardium caused few subjective cardiac symptoms, as might be expected. In fact, frequently there

were no objective signs. Nine of the patients in this series showed no cardiac murmurs, diastolic murmurs developed in 7 while they were under observation, and the remaining 3 had valvular murmurs on admission to the hospital. One of these 3 patients had been under observation for several years and was thought to have had double mitral and aortic lesions of rheumatic origin, no change was detected in the quality of the murmurs, despite an acute bacterial engraftment on both valves.

The size and shape of the cardiac dulness were usually within normal limits. One patient showed an enlargement which was not explainable by a history of antecedent cardiac disorder or of a long-standing illness.

Abnormalities of rhythm were infrequent. It has been a clinical dictum for many years that fibrillation spares a patient from bacterial endocarditis. One patient (case 14) presented this coincidence, although it could not be ascertained whether or not the obtunded rhythm preceded the onset of the pneumonia. Another patient showed gallop rhythm terminally.

Petechiae were observed in only 5 patients (26.3 per cent). This is in striking contrast to the incidence of petechiae in endocarditis due to *Streptococcus viridans*. If petechiae are of embolic origin, the relative infrequency of this observation is all the more significant because embolic phenomena in viscera were noted regularly at necropsy. Clinically, two cerebral embolisms and one femoral embolism were observed.

Only 1 patient in this whole series had jaundice, and the jaundice in this instance, due to obstruction of the common duct, was present many months before there was evidence of endocarditis. It is surprising that whereas jaundice is seen in 5 to 10 per cent of the patients with pneumonia, it is rarely recorded as a complication of endocarditis.

Clubbing of the fingers or toes was not noted in this series. In view of the acuteness of pneumococcic endocarditis, it does not seem remarkable that acropachy is seldom observed as an accompanying sign.

A palpable spleen, observed so frequently in subacute bacterial endocarditis, was never recorded in the series. It is not improbable that an enlarged spleen is frequently overlooked because of the patient's acutely ill condition.

Pyarthrosis occurred in 2 patients (10.5 per cent). This finding also may conceivably be overlooked in a very ill patient. In both cases the knee joint was involved, in 1 case a shoulder joint also contained pus. As might be expected, the organism within the joint was of the same type as the one in the endocardial vegetation.

ACCESSORY EXAMINATIONS

Culture of the blood is the most important and indispensable method of confirming the diagnosis of pneumococcic endocarditis. Blood cultures were made for every patient. Only 2 failed to show growth, these

Case	Sex	Race	Age	Hospital Residence	Bacteriologic Data			
					Sputum	Blood	Vegetation	Other Data
1	M	N	21	12/14/35-1/1/36	12/18 VI	12/28 VI		Spinal fluid, 12/29 VI
2	M	W	69	1/4/36-1/30/36	1/6 I	1/20 I 1/22 I	5/11/37 I 12/11/37 I	
3	F	N	90	12/8/36 12/11/36	12/10 XI 12/11-XI	12/8 XI (77) 12/11 XI		Spinal fluid, 12/10 XI, fluid from knee joint, 12/9 XI
4	M	N	47	12/31/36 1/3/37		12/31-XX 1/1 XX (134)		Spinal fluid, 12/31-XX
5	M	N	23	1/5/37 2/13/37	1/5 I	1/5 I (500) 1/12 neg	5/11/37 I	Pleural fluid, 1/14 I
6	F	W	16	1/8/37 1/9/37	1/8 XXIX	1/8 neg	1/9 XXIX	
7	F	W	46	1/10/37 1/12/37	1/10 II	1/10 II 1/12 II		Pericardial fluid, 1/12 II spinal fluid, 1/12 II
8	M	W	50	2/10/37 3/5/37	2/10 V	2/10 neg 2/11 neg 2/16 neg 2/23 neg 2/27 V 3/1 V 3/3 V (25)	3/5 V 5/11 V	Spinal fluid, 3/5-V.
9	M	W	51	2/15/37 2/25/37		2/19 IX 2/20 IX (24) 2/22 IX	5/11 IX	
10	M	W	46	3/24/37 3/28/37	3/26 VIII ‡	3/26 V 3/27 V (800)		Spinal fluid, 3/26 V
11	F	W	60	4/26/37 5/9/37	5/6 VIII 5/7 VIII	5/7 VIII (4 800) 5/8 VIII (440) 5/9 VIII (2)	5/9 VIII	Spinal fluid, 5/9 VIII
12	M	N	40	5/3/37	5/3 IV ‡	5/3 neg	5/10 IV 5/11 IV	Spinal fluid, 5/3 IV
13	M	N	47	4/5/37 4/30/37	4/5 VII 4/6 VII	4/5 VII 4/6 neg 4/7 neg 4/8 VII (36) 4/12 neg 4/17 VII (4) 4/18 neg 4/19 VII (2) 4/20-VII (23) 4/22 VII (35) 4/24 VII (25) 4/26 VII (1,500) 4/28 VII (560)	5/10 IV 5/11 IV 5/1 VII	Spinal fluid, 4/19 neg 4/20 neg 4/22 VII 4/29 VII
14	M	N	56	5/18/37 5/19/37	5/18 IV	5/18 IV (16,880) 5/19 IV (15,000)		
15	M	N	46	8/10/37-8/18/37	8/10 VIII	8/10 VIII (1 600) 8/11 VIII (320) 8/12 VIII (60) 8/13 VIII (800) 8/14 VIII (300) 8/15 VIII 8/16 VIII (408)	8/18 VIII 9/9 VIII	Pleural fluid, 8/10 VIII 8/11 VIII
16	F	W	41	1/8/37 1/25/37	1/8 V	1/8 V 1/11 neg 1/19 neg 1/21 V (25) 1/23 V		Pleural fluid, 1/19 V
17	M	N	70	2/20/37 3/2/37	2/21 XII	2/21 XII 2/22 XII (160) 2/23 XII (35) 2/24 XII 2/25 neg 2/26 neg 3/1 XII		
18	M	W	41	3/2/37 3/12/37	3/2 V 3/3 V 3/5 V	3/2 V (490) 3/3 V (450) 3/5 V (60) 3/6 V (115) 3/8 V (88) 3/9 V (356) 3/10 V 3/11 V (350)		Fluid from knee joint, 3/10 V from shoulder joint, 3/10 V
19	M	W	55	3/25/37 3/31/37		3/26 V (15) 3/29 V (25) 3/30 V (5)		Spinal fluid, 3/30 V

* The roman numerals indicate the type of pneumococci found. The numbers in parentheses refer to the number of colonies per cubic centimeter.

† The Wassermann or Kahn test gave a positive reaction.

‡ Culture of material obtained by swabbing the throat.

Clinical Data			Necropsy		Observations
Leukocytes	Cardiac Murmurs	Embolie Phenomena	Endocardial Vegetations	Pneumonia	Other Data
12,200	†		Aortic	Lobar and lobular	Meningitis, perivascular scars in myocardium (rheumatic?)
16,000 20,000	Systolic and diastolic over base, 1/20	Petechiae	Aortic	Lobular	Myocardial degeneration
11,100	Systolic at apex		Mitral	Lobular	Meningitis, pyarthrosis, metastatic abscess and acute infarction of kidney
19,000 26,000	Systolic at apex†	Hemiplegia	Mitral	Lobular	Meningitis, cerebral infarction and abscesses, splenic abscesses, syphilitic aortitis
15,000 49,000	†		Aortic	Lobar	Purulent pericarditis, empyema, mycotic aneurysm of aorta, syphilitic aortitis
20,200		Petechiae	Mitral and aortic	Lobar and lobular	Meningitis, abscess of spinal cord and myocardium, pulmonary embolism
9,000 10,000		Petechiae	Aortic	Lobar and lobular	Meningitis, purulent pericarditis, empyema, myocardial degeneration and fibrosis
13,000 48,000	Diastolic over base, 2/23	Hemiplegia	Aortic and tricuspid	Organizing lobar	Meningitis, fibrinopurulent pleuritis, pulmonary infarction mural thrombosis, acute diffuse glomerulonephritis
8,000 14,000		Petechiae, femoral embolism	Mitral	Lobar	Meningitis, splenic and renal emboli, myocardial abscesses, rheumatic scar of mitral valve adenocarcinoma of ampulla of Vater
12,600		Petechiae	Mitral	Lobar and lobular	Meningitis, panophthalmitis, renal and splenic infarcts
9,000 16,000	Aortic diastolic, apical systolic and diastolic before entry		Mitral, aortic and about foramen ovale	Lobular	Meningitis, pulmonary infarctions, healed rheumatic endocarditis of mitral and aortic valves, pyelonephritis
17,000			Aortic	Resolving lobar	Meningitis, focal embolic nephritis
5,000 23,000	Systolic and diastolic, loudest at apex, 4/29		Aortic	Resolving lobar	Meningitis, miliary abscess of kidney, acute focal myocarditis myocardial fibrosis
7,000 8,300	†		Aortic	Lobar	Syphilitic aortitis acute pyelonephritis
14,000 35,000			Tricuspid	Lobular	Empyema
15,000 17,000	Systolic and diastolic over base and apical systolic, 1/19		No necropsy, clinical diagnosis of lobar pneumonia followed by empyema and acute aortic valvulitis		
	Diastolic over base, 2/28		No necropsy, clinical signs of lobar pneumonia signs of aortic regurgitation appeared one week after entry		
6,000 17,000	Diastolic over base, 3/6		No necropsy clinical diagnosis of lobar pneumonia which began to resolve pyarthrosis developed after signs of aortic regurgitation appeared		
9,000 10,000	Diastolic over base, 3/28		No necropsy clinical diagnosis of unresolved lobar pneumonia meningitis followed signs of aortic regurgitation		

patients having died after a few hours in the hospital, and the etiologic factor was proved by culture from the valves at necropsy. Colony counts were made for all blood cultures. The number of colonies had no prognostic significance. The highest count exceeded 16,000 colonies per cubic centimeter. The type specificity of the organisms was always striking. In other words, examination of the sputum, joint fluid, empyema pus or cerebrospinal fluid or culture material from the lung (by suction) and throat almost invariably disclosed a pneumococcus of the same type as the organism found in the blood stream or in the vegetation. A single exception occurred in case 10, in which type VIII pneumococci were found in a single culture of material from the throat, whereas several blood cultures and the cerebrospinal fluid showed type V pneumococci.

An examination of the various components of the blood usually disclosed important deviations from the normal, but there was no typical pattern. As a rule leukocytosis was present, as in other pneumococcic infections, although this was not always striking. Two patients had white blood cell counts of 10,000 or less. The great majority showed counts between 10,000 and 20,000, six counts were in excess of 20,000, the highest being 48,000. There was no apparent correlation between the number of circulating leukocytes and the clinical data, it may be significant, however, that the patient with the lowest count (8,300) had overwhelming bacteremia (15,000 colonies or more per cubic centimeter). There was invariably associated with the leukocytosis a relative increase in the number of polymorphonuclear neutrophils. Anemia of the hypochromic type was present in about half the cases. This became apparent in those cases in which the disorder was of longer duration, as might be expected. Urinary findings were those of an acute febrile illness. Albuminuria was noted in half the patients. Despite microscopic and gross evidence of infarction at necropsy, hematuria was not observed in any cases. White blood cells and casts were found occasionally.

Electrocardiographic tracings were made for 5 patients. One showed a normal tracing, despite clinical signs of acute aortic insufficiency. The others were interpreted as indicative of myocardial disease of varying degree. One tracing (case 11) showed a PR interval of 0.22 second, although the interval two months previously had been 0.16 second. White¹² recorded this as an infrequent finding in acute bacterial endocarditis. Segal¹³ also found this to be more commonly observed in

12 White, P. D. *Heart Disease*, ed. 2, New York, The Macmillan Company, 1937.

13 Segal, M. S. *Bacterial Endocarditis with Special Reference to Cardiac Irregularities. Clinical and Pathological Study of One Hundred and Ninety-One Cases*, *Am Heart J* **11** 309, 1936.

cases of involvement of the aortic valve than in cases of mitral involvement

Pneumococcic endocarditis in our experience usually pursued an acute and rapid course. Obviously, it is practically impossible to ascertain the exact date of onset. In 17 of the 19 cases the disorder terminated within five weeks of the onset of the acute pneumococcic infection, of which the endocarditis was presumably a complication or sequel. One patient gave a history of lobar pneumonia at least five months previous to entry, with uneventful convalescence, then there was a gradually increasing feeling of malaise, interrupted suddenly by chills and fever. Judging from clinical data, the estimated duration of the process exceeded two weeks in only 1 instance. Fortunately it was

TABLE 2—*Types of Pneumococci in Nineteen Cases of Pneumococcic Endocarditis*

Type	Incidence	Type	Incidence
I	2	VIII	2
II	1	IX	1
IV	2	XI	1
V	5	XII	1
VI	1	XX	1
VII	1	XXIX	1

TABLE 3—*Necropsy Data for Patients with Pneumococcic Endocarditis*

Involvement	No. of Cases	Involvement	No. of Cases
Aortic	7	Left side of heart	13
Mitral	4	Right side of heart	1
Tricuspid	1	Both sides of heart	1
Aortic and mitral	2		
Aortic and tricuspid	1		

possible to observe 5 patients throughout the primary and secondary phases of the infection, cultures were made at frequent intervals after spontaneous or induced defervescence of the fever, in 1 instance the blood culture again gave positive results fourteen days before death. The actual duration of the endocarditis probably is greater than the period indicated by pneumococcemia but less than the total period of the illness.

The disease terminated in meningitis in 13 (68.4 per cent) of the cases. Only 1 of the 6 remaining patients failed on postmortem study of the calvarium or of the spinal fluid to show evidence of meningitis. This patient also was the only one to show purely right-sided endocarditis, consequently, the incidence of meningitis may well have been higher, especially since there was such a preponderance of left-sided cardiac lesions.

PATHOLOGIC OBSERVATIONS

The vegetations of pneumococcic endocarditis vary considerably in size, color and distribution. The great majority of the vegetations show ulceration, either grossly or microscopically, case 13 demonstrated ulceration which progressed to actual rupture of the valve. The vegetations vary in size from papilliform or cauliflower-like masses, 1.5 cm in diameter, to mere excrescences of the endothelium. They are usually friable. They are grayish red, or sometimes there is a mottling of red and gray. The distribution of lesions in this disease is shown in table 1. Sometimes the pneumococcus attacks the endocardium elsewhere, leaving the valves intact. In case 11 there were vegetations around the foramen ovale in addition to those on the valves. The predilection of the pneumococcus for the left side of the heart is not surprising, since in the great majority of instances the portal of entry is probably the lung. The site of election is shown in the table. The incidence of involvement of the aortic valve is striking, no plausible reason is apparent, although Netter, Preble and Thayer found a similar election. Lesions on the pulmonary valve, infrequently seen in any type of endocarditis, were not observed, although such lesions have been reported.

The immediate effects of the endocarditis on the heart itself were difficult, if not impossible, to determine. There was moderate hypertrophy of the myocardium in more than two thirds of the cases in which necropsy was performed, but coexistent cardiovascular disease precluded any conclusion concerning the cause. It may be significant, however, that the largest heart (case 15), weighing 700 Gm, was that of a patient with little evidence of other disease yet showing pure tricuspid endocarditis with dilatation of the ring. Mural thrombi were present in only 3 instances. One vegetation eroded the aortic intima to form a small mycotic aneurysm.

Pneumonia was present in all the 15 cases in which necropsy was performed. It was lobar in 6, lobular in 5 and mixed in 4. In only 2 was there evidence of resolution, in 1 case organization was taking place. In case 11 the pneumonia probably was entirely secondary to infarction.

While pneumococcic infections are notoriously prone to cause purulent foci, the incidence of such suppurative processes was striking in this group of cases. Only 2 of the 15 patients failed to reveal such foci, and in neither of these cases was complete necropsy performed. Although meningitis occurred most frequently, a multiplicity of purulent focal processes was seen in more than 50 per cent of the cases at necropsy. These foci included empyema of the pleural cavity, pericarditis, pyarthrosis, abscesses of the myocardium, abscess of the brain, abscess of the spinal cord and focal embolic nephritis.

Although the spleen was never palpated clinically, it was almost invariably enlarged at necropsy. Usually it appeared as a moderately enlarged organ with a friable pultaceous pulp, occasionally follicular markings were lost.

THERAPY

In view of the fact that pneumococcic endocarditis is invariably reported as a disease of hopeless prognosis, discussion of modes of therapy may seem futile. However, Wadsworth,⁹ after observations of the process in horses, said he was confident that he saw scars of old healed inflammations of the valves, the implication being that they were due to the pneumococcus. If one may make an analogy between this type and other types of acute bacterial endocarditis,¹⁴ it is not unreasonable to suspect that at least a small percentage of patients recover. Preble³ reported on 4 patients, including 2 of his own, who recovered, 1 of them presented all the findings for an antemortem diagnosis and must certainly be considered as representing a case of genuine pneumococcic endocarditis. Lanby and Coffin¹⁵ reported the only other instance of recovery since Preble's report, but here the diagnosis is by no means so convincing. The authors treated their patients with antipneumococcus serum and later with vaccine. Immunologic studies were not made of the patients of this series, but the rationale of serum and vaccine therapy does not seem well founded. Wadsworth demonstrated acute active vegetations in horses which were producing potent therapeutic serum. Three of the patients of the present series (cases 5, 13 and 16) received sufficient serum to sterilize the blood stream temporarily, yet they subsequently had endocarditis. Horder¹⁶ reported the employment of diathermy without encouraging results. He also reported the use of roentgen therapy with success in 1 case. One of the patients in the present series (case 18) was given high voltage roentgen therapy over the precordium, with no apparent effect on the course. Since there is some evidence that certain strains of pneumococci may have a thermal death point compatible with the maintenance of human life, 1 patient (case 8) was treated by hypertherm exposures. This treatment did not prove successful, the cooperation was poor and the program was not carried to its completion. Another patient (case 15) was treated with sulfanilamide, he was given the drug for seven days in large doses, although

14 Perry, M. W. Gonorrheal Endocarditis with Recovery. A Case Report, *Am J M Sc* **179** 599, 1930, Further Note on a Case of Gonorrheal Endocarditis with Recovery, *ibid* **185** 394, 1933. Hamman, L. Healed Bacterial Endocarditis, *Ann Int Med* **11** 175, 1937.

15 Lambry, C., and Coffin, M. Endocarditis infectieuse primitive a pneumocoques terminee par la guerison, *Bull et mém Soc med d hôp de Paris* **52** 281, 1928.

16 Horder. Septic Endocarditis, *Lancet* **2** 174, 1936.

the concentration in the blood did not exceed 8 mg per hundred cubic centimeters until the day before death, when it was 17 mg. Far from sterilizing the blood stream, it actually did not change the colony count appreciably. As it was found that solution of formaldehyde and other preservatives failed to kill the pneumococcus embedded in vegetations post mortem, it scarcely seems likely that a nonspecific drug, so innocuous to tissue as sulfanilamide, would effect the desired result.

In conclusion, the problem of mode of therapy seems to be frankly one of prevention. Others have also been unimpressed by serum or drug therapy. Wadsworth's finding that horses may produce potent therapeutic serum yet may have endocarditis is discouraging to the prospects of serum therapy. However, that should not be a contraindication to large doses of specific serum when the diagnosis is once made. Since endocarditis has its origin in bacterial invasion of the blood stream and since potent therapeutic serums are today available, prompt and vigorous serum treatment of acute pneumococcic infection should be instituted. In addition to serum therapy, surgical eradication or at least surgical drainage of accessible purulent foci should be employed without hesitation, for such foci constitute a constant potential source for invasion of the blood stream. Those two methods of attack on acute pneumococcic infection should do much to decrease the incidence of this complication markedly.

CONCLUSIONS

Acute endocarditis occurring in the course of pneumococcemia is probably always due to the pneumococcus.

Acute endocarditis is a considerably more frequent complication of pneumococcic sepsis than is generally believed.

Pneumococcic endocarditis may be diagnosed ante mortem in about 50 per cent of the cases if certain laboratory facilities are available.

Pneumococcic endocarditis usually occurs as a complication or sequel of pneumococcic pneumonia, runs an acute course, attacks especially the valves of the left side of the heart, is characterized by embolic phenomena and terminates in the majority of instances in purulent meningitis.

As serum and drug therapy of pneumococcic endocarditis has been almost uniformly unsuccessful, therapeutics should be largely prophylactic, namely, the prevention of bacteremia by means of potent specific serum and the removal or drainage of purulent foci.

PRIMARY BENIGN TUMOR OF THE HEART OF FORTY-THREE YEARS' DURATION

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Tumors of the heart are rare. A large series of autopsy reports (approximately 40,000 cases) show that metastatic growths in the heart occur in approximately 0.5 per cent of cases, whereas primary tumors are found in 0.03 per cent (Yater¹ and Mead²). On the other hand, studies of cases of malignant growth with disseminated metastases reveal an incidence of about 7.5 per cent in cases of cardiac involvement (Yater,¹ Burke³). Metastatic tumors have been reported as diagnosed during life in only 10 cases, the first by Roesler,⁴ in 1924, and all the others since 1930 (Heninger,⁵ Willius and Amberg,⁶ Fishberg,⁷ Schnitker and Bailey,⁸ Doane and Solis-Cohen,⁹ Smith¹⁰). Such tumors may involve any part of the heart, but especially the right auricle. They have been described as arising from almost any type of malignant tumor anywhere in the body. Usually they produce no symptoms and are found accidentally at autopsy. Symptoms or signs of cardiac involvement in a case of known malignant involvement may

1 Yater, W. M. Tumors of the Heart and Pericardium, *Arch. Int. Med.* **48** 627 (Oct.) 1931.

2 Mead, C. H. Metastatic Carcinoma of the Heart, Secondary to Primary Carcinoma of the Lung, *J. Thoracic Surg.* **2** 87, 1932.

3 Burke, E. M. Metastatic Tumors of the Heart, *Am. J. Cancer* **20** 33, 1934.

4 Roesler, O. A. Vier seltene Herzbefunde. Ein Beitrag zur Herzdiagnostik, *Zentralbl. f. Herz- u. Gefasskr.* **16** 261, 1924.

5 Heninger, B. R. Clinical Aspects of Pericardial Metastasis, *Ann. Int. Med.* **7** 1359, 1934.

6 Willius, F. A., and Amberg, S. Two Cases of Secondary Tumor of the Heart in Children, in One of Whom the Diagnosis Was Made During Life, *M. Clin. North America* **13** 1307, 1930.

7 Fishberg, A. M. Auricular Fibrillation and Flutter in Metastatic Growths of Right Auricle, *Am. J. M. Sc.* **180** 629, 1930.

8 Schnitker, M. A., and Bailey, O. T. Metastatic Tumor of the Heart. A Case Diagnosed During Life, *J. A. M. A.* **108** 1787 (May 22) 1937.

9 Doane, J. C., and Solis-Cohen, L. Symmetrical Adrenal Neuroblastoma Metastasizing to the Right Auricle, *J. A. M. A.* **109** 578 (Aug. 21) 1937.

10 Smith, D. S. Neoplastic Involvement of the Heart, *J. A. M. A.* **109** 1192 (Oct. 9) 1937.

suggest an antemortem diagnosis. The cardiac disturbances most commonly noted have been arrhythmias, bloody pericardial effusion, localized edema in the face, neck or hands, excessive dyspnea, oppression in the chest, and the acute onset of signs of congestive heart failure. Naturally, the symptoms and signs depend on the size and the location of the tumor.

Primary tumor of the heart may be either malignant or benign. Only 2 cases have been reported in which the diagnosis was made before death, in both the tumor was malignant. The first case was reported by Barnes, Beaver and Snell,¹¹ in 1934. Their patient, a woman aged 62, with symptoms and signs of acute pericarditis, had pain in the region of the deltoid muscle. Biopsy revealed the cells of a malignant tumor, and later an electrocardiogram disclosed complete auriculoventricular dissociation. Autopsy showed rhabdomyosarcoma of the right auricle, pericardium and right ventricle.

In the case reported by Shelburne,¹² in 1935, the diagnosis was made on the basis of finding a bloody pericardial exudate in a patient who showed no fever or signs of tuberculosis. The electrocardiogram showed partial bundle branch block. Four days later there were signs of acute cardiac decompensation. At autopsy, sarcoma of the pericardium was demonstrated.

Recently, Shelburne, as well as other authors,¹³ have erroneously quoted Goettel¹⁴ as having credited Pavlowski¹⁵ with reporting the only benign tumor of the heart ever diagnosed before death. Actually Pavlowski¹⁶ reported a case of myxoma of the left auricle in which autopsy was performed. Like other authors who have reported cases of primary tumor of the heart, he reasoned backward from the autopsy protocol and showed how and why the symptoms were produced. His own antemortem diagnosis was *dilatatio cordis* due to a chronic char-

11 Barnes, A. B., Beaver, D. C., and Snell, A. M. Primary Sarcoma of the Heart. Report of a Case with Electrocardiographic and Pathological Studies, *Am Heart J* **9** 480, 1934.

12 Shelburne, S. A. Primary Tumors of the Heart, with Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis Before Death, *Ann Int Med* **9** 340, 1935.

13 Gilchrist, A. R., and Miller, W. G. Paroxysmal Auricular Tachycardia Associated with a Primary Cardiac Tumor, *Edinburgh M J* **43** 243, 1936. Yater¹, Mead², Schnitker and Bailey³.

14 Goettel, L. Ein Fall von primären Herztumor, *Deutsche med Wchnschr* **45** 937, 1919.

15 Pavlowski, R. A. Ueber Herzthromben. Gestielte Thromben oder "wahre Polypen" des Herzens, *Ztschr f klin Med* **26** 482, 1894.

16 Pavlowski, R. Beitrag zum Studien der Symptomatologie der Neubildungen des Herzens. Polypöse Neubildungen des linken Vorhofs, *Berl klin Wchnschr* **32** 393, 1895.

acteristic cause Where it was and of what nature could not be determined He stated that it was something out of the ordinary

A primary tumor may occur in any portion of the heart The rarest location is on the valves Such a tumor is usually small and of no clinical significance (Ferel¹⁷) The most frequent site of a primary tumor is the left auricle, in contrast to a metastatic tumor, which most often invades the right auricle However, a tumor may be present in the wall of any of the cardiac chambers (Karrenstein¹⁸) and may occur at almost any age In children rhabdomyoma occurs with tuberous sclerosis and with other signs of congenital defects (Fiddler¹⁹) The first rhabdomyoma in an adult was reported in 1928 by Bradley and Maxwell²⁰ A tumor may be present without any cardiac manifestations, and if symptoms or signs occur they depend, as has been remarked, on the size and the location of the tumor One of the most interesting tumors described in the literature is the pedunculated myxoma of the left auricle which drops into the auriculoventricular opening and intermittently occludes the mitral valve (Pavlovski,¹⁶ and Houck and Bennett²¹) In other cases the conduction system is involved, and arrhythmia occurs (Wegman and Egbert²²)

All primary tumors of the heart are of mesoblastic origin—fibroma, myxoma, sarcoma, rhabdomyoma In much of the earlier literature one finds a discussion of the differentiation between cardiac thrombi and myxomas, some of the earlier so-called tumors were actually thrombi (Chiari²³ and Lymburner²⁴) With the better technical facilities available for microscopic study in recent years, there is no real difficulty today in differentiating between these two conditions

17 Ferel, F C Two Cases of Primary Neoplasm of the Cardiac Valves, *Internat Clin* **4** 147, 1919

18 Karrenstein Ein Fall von Fibroclastomyom des Herzens und Kasuistisches zur Frage der Herzgeschwulste, besonders der Myxome, *Virchows Arch f path Anat* **194** 127, 1908

19 Fiddler, R S, Kissane, R W, and Koons, R Primary Fibrosarcoma of the Heart, *Am Heart J* **13** 736, 1937

20 Bradley, E B, and Maxwell, E S Primary Neoplasms of the Heart Report of an Unusual Case, *J A M A* **91** 1352 (Nov 3) 1928

21 Houck, G H, and Bennett, G A Polypoid Fibroma of the Left Auricle (So-Called Cardiac Myxoma) Causing a Ball-Valve Action, *Am Heart J* **5** 787, 1930

22 Wegman, M E, and Egbert, D S Congenital Rhabdomyoma Associated with Arrhythmia, *J Pediat* **6** 818, 1935

23 Chiari, H Myxom des rechten Vorhofs Ploetzlicher Tod durch Geschwulstembolie der Lungenschlagader, *Centralbl f allg Path u path Anat* **52** 291, 1931

24 Lymburner, R M Tumors of the Heart Histological and Clinical Study, *Canad M A J* **30** 368, 1934

As for the clinical history and the intra vitam diagnosis of cardiac tumors, it must be admitted that practically all the information so far published has been based on ex post facto reasoning. Meroz²⁵ reviewed the subject in 1917, attempting to show from a casuistic analysis of some cases how the diagnosis should be made. Yet the first metastatic malignant tumor of the heart was diagnosed in 1924 (Roesler⁴) and the first primary malignant tumor in 1934 (Barnes, Beaver and Snell¹¹), as yet no benign primary tumor has been diagnosed during life. Siegel and Young²⁶ studied the electrocardiographic changes in all cases of cardiac tumor reported up to 1933 and concluded that there was great similarity of the electrocardiographic findings in cases of tumor of the heart and in myocardial changes from other causes, especially coronary disease. Minor differences were noted, especially the lack of reciprocal direction of the T wave in leads I and III and the failure to show deviation from the isoelectric level in the ST segment. They also suggested that the electrocardiographic changes in cases of tumor gave some evidence as to the location of the neoplasm in the heart. These findings certainly are not specific.

REPORT OF A CASE

The patient was born in 1872 and died on Dec 7, 1935. Friends of his youth stated that although he led an active life for his first twenty years, "he had to be careful of his health." There was no history of rheumatism or of infection. Apparently during his youth he was not seriously incapacitated, and in his late teens he was accepted for the only life insurance policy he ever obtained. He had a curvature of the spine, which progressed steadily as he grew older. In 1892 he consulted the late Dr. Otto L. Schmidt, in Chicago, when the diagnosis of "heart trouble" was made. According to the patient's wife, he was at that time compelled to live a carefully regulated life but was subsequently able to play golf and to take long walks. For many years his life was not greatly disturbed. In 1917, at the age of 45, he consulted Dr. Walter Hamburger, who has placed at my disposal all his notes, which I am freely using in reconstructing the case history. From 1923 until his death the patient was under the care of Dr. Binswanger and myself. In no previously reported case has a patient with cardiac tumor lived so long or offered such a good opportunity for detailed study during life. The diagnosis was not made ante mortem. I repeatedly expressed the opinion that we were dealing with an unusual type of heart disease, but neither I nor any of the consultants suggested the correct diagnosis.

When the patient was first seen by Dr. Hamburger, he was recovering from a severe infection of the upper respiratory tract and complained of edema of the ankles. The urine contained much albumin and many casts, the heart was enlarged to the left. A soft diastolic murmur was heard along the left border of the sternum. The systolic blood pressure was 118. Later the character of the

25 Meroz, E. A Clinical Study of Three Cases of Primary Tumor of the Heart, *Internat Clin* 4 331, 1917.

26 Siegel, M. L., and Young, A. M. Electrocardiographic Findings in Tumors of the Heart, with a Report of a Case, *Am Heart J* 8 682, 1933.

murmur changed, so that the notes at various times read "A soft postdiastolic murmur to the left of the sternum" "A soft presystolic-diastolic murmur"

In May 1920 the patient complained of shortness of breath. Extrasystoles were noted for the first time. The albumin and casts that were found in the urine in 1917 soon disappeared, but in 1920 they recurred. In June 1921 dyspnea was again present. The left border of the heart was found to be 2 fingerbreadths beyond the left nipple. The soft postdiastolic murmur was louder. The liver was enlarged but was not tender. Pitting edema of the ankles was noted. In January 1922 the liver was a full handbreadth below the costal margin. The heart measured 4 cm to the right and 12.5 cm to the left of the midsternum. The murmur was "soft, faint, presystolic, late in diastole and continuing to the first tone at the apex." The liver was still enlarged and not tender. The spleen was not felt. The renal function was not impaired.

It is to be emphasized at this point that the liver constantly remained enlarged a full handbreadth below the costal margin and was firm, round and never tender.

When the patient came under the care of Dr. Binswanger and myself, in 1923, he showed definite decompensation, and he complained of shortness of breath and edema of the ankles. These two symptoms were his main complaints at this time and later. Cyanosis, cough and rales in the chest were never prominent. He was not incapacitated for work. The examination showed, in brief, marked kyphoscoliosis and marked cardiac enlargement in all directions. The murmur was loud, was heard over the whole precordium and was definitely systolic. The systolic blood pressure varied between 130 and 140 and remained fairly constant all through his life. There was fibrillation at that time, and this also remained constant until his death.

Then began a series of remarkable changes in his condition. He made a spectacular recovery from this attack and was well and active until September 1925. Then another episode of dyspnea and edema occurred. Through 1926 and 1927 he worked full time, with only an occasional examination for routine check-up and with no noteworthy changes. In January 1928 he had pneumonia, involving the bases of both lungs, he was almost moribund but managed to survive. He remained in excellent condition until November 1929. Then symptoms of congestive failure recurred, followed by the usual recovery, which lasted until May 1932. From this time on more or less constant dyspnea, pedal edema and oppression in the chest with anginal pains were present. Although he was not confined to bed, there was definite and increasing restriction of his activity.

A new condition arose in 1927, when he began to complain of occasional precordial pains. At times these were typical anginal pains on effort, at other times they would occur when he was quietly sitting in bed.

In 1933 he began to complain of pain in the lower left quadrant of the abdomen, associated with frequent small stools containing pus and blood. Parasites were never found. These symptoms increased in severity.

On Dec. 6, 1935, severe acute abdominal pains developed, with bloody diarrheal stools. A barium sulfate enema revealed marked tubular encroachment of the sigmoid flexure, which resembled an inflammatory rather than a neoplastic lesion. Surgical intervention was considered, but the patient's general condition was too poor. Death occurred the next day, following symptoms of a ruptured intestine with peritonitis.

I have purposely avoided discussion of either the electrocardiograms or the roentgenograms because it seems more graphic to describe them separately. The roentgen examinations date from August 1921, when marked cardiac enlargement and some bulging of the arch of the aorta were noted.

In February 1922 there was a marked increase in the transverse diameter, and the aorta was broad. The right border of the heart was far beyond the usual normal limits, but there was marked scoliosis, which would account in part for the position of the heart. The left border of the heart was rather straight. The left ventricle appeared swollen.

In August 1922 the heart was 16.5 cm in diameter and the chest 30 cm.

In October 1925 the heart was 18.8 cm in diameter. It appeared swollen as in cases of pericarditis with effusion or myocarditis. The aorta was broad and dilated.

In December 1927 the heart was 20.4 cm in diameter.

In October 1929 the heart was 21 cm in diameter.

In May 1932 the heart was 22 cm in diameter. What appeared to be the right border had a rippled contour, suggesting pericardial disease.

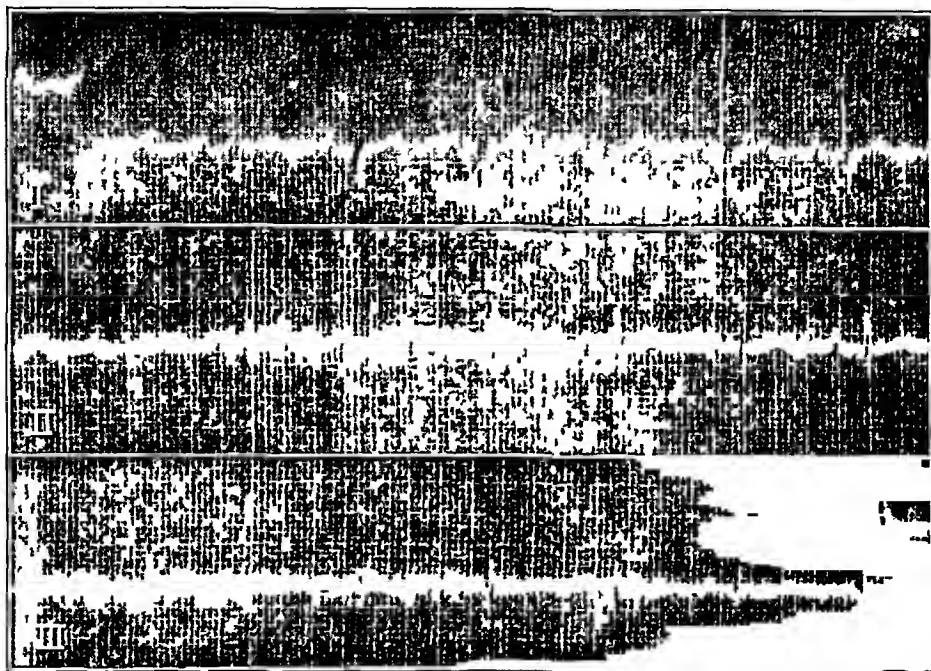


Fig 1—Sept 18, 1919. A normal electrocardiogram.

On Dec 6, 1935, fluoroscopic examination showed tremendous cardiac enlargement.

It is greatly to be regretted that, owing to legal restrictions on the preservation of x-ray films, none of the roentgenograms of this patient are available for reproduction. Measurements are lacking to substantiate our impression that the increase in the width of the right border of the heart noted in 1922 was constantly present. In fact, it seems in retrospect that not enough attention was paid by us to the changes in the right border.

We are able to present an unusual series of electrocardiograms, which graphically show the progressive cardiac changes (figs 1 to 6).

Postmortem Examination—A complete autopsy was performed one hour post mortem by Dr Otto Saphir (Michael Reese Hospital, Chicago). The pathologic diagnosis was as follows: primary adenocarcinoma of the rectum with stricture formation, marked chronic and acute polypoid and ulcerating colitis and perfora-

tion of the upper portion of the sigmoid flexure, acute serofibrinopurulent peritonitis, primary myxoma of the right auricle, marked dilatation and hypertrophy of the right auricle, generalized arteriosclerosis, severe coronary sclerosis, slight narrowing of the ostium of the right coronary artery, arteriosclerosis of the aortic valve, fibrosis of the myocardium, chronic passive hyperemia of the liver [weight, 1,600 Gm], cloudy swelling of the liver and kidneys, arteriosclerotic scars of the kidneys, enlargement of the prostate, fibrosis of the spleen, edema of the ankles, and marked scoliosis of the vertebral column

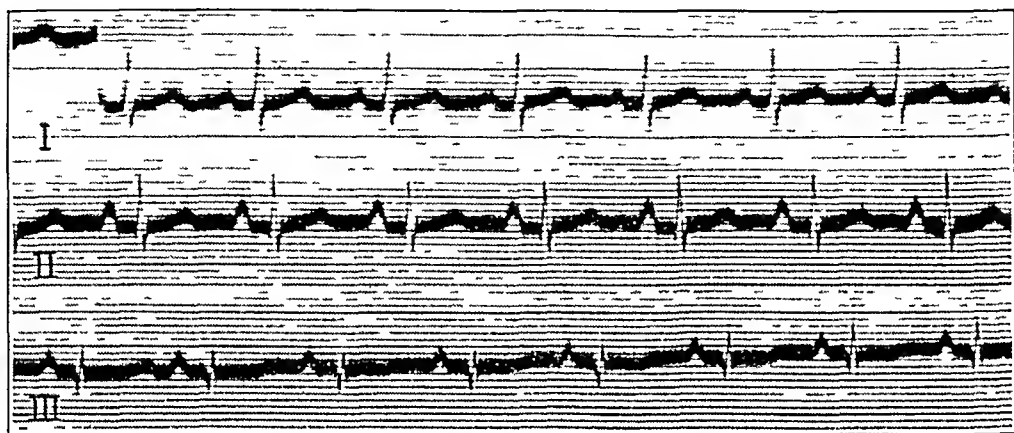


Fig 2—Jan 11, 1921 P₂ and P₃ are extremely high and notched

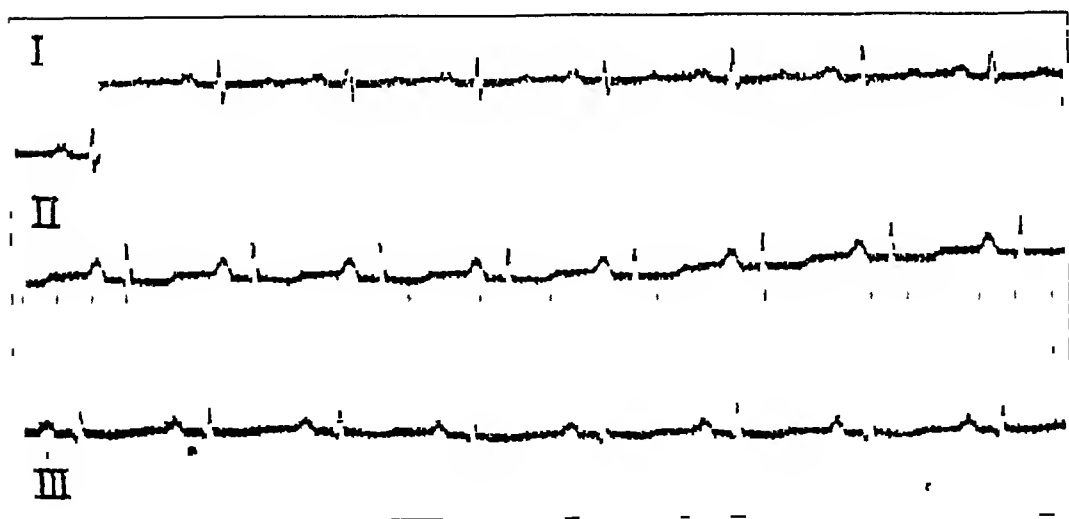


Fig 3—Aug 14, 1922 P is enlarged and notched in all leads T₂ is diphasic

All details except those referring to the cardiac condition are omitted

The heart was markedly enlarged and weighed 750 Gm. The epicardium was slightly granular over the region of the right auricle. However, the greater bulk of the heart seemed to be in the right auricle, the left ventricle was apparently no larger than usual. The right auricle contained a large spherical mass, about the size of an orange (measuring about 8 by 9 by 10 cm). It was attached to the endocardium of the interauricular septum and almost completely filled the auricle. This tumor was semifirm, with a slightly gelatinous consistency. Through the upper layers of the mass, small, irregular, firm calcific masses could be felt. The

color of the tumor varied from a semitranslucent yellow-green to blood red. Sections taken from the tumor showed it to be of jelly-like consistency. The cavity of the right auricle was markedly dilated and its wall thickened. The endocardium of the rest of the heart showed no change. The cardiac valves showed no change with the exception of the aortic valve, which was markedly thickened.

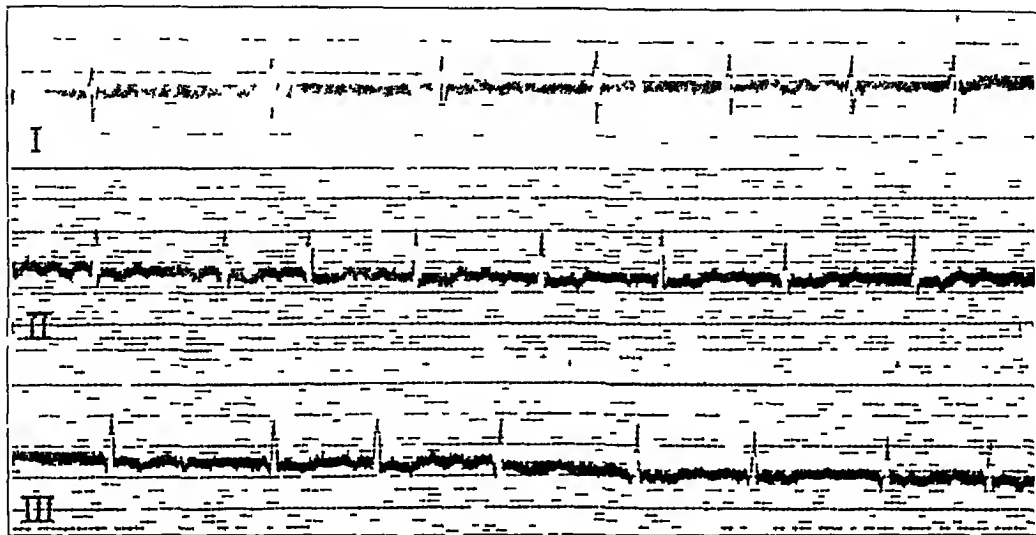


Fig 4—Oct 12, 1925 The electrocardiogram shows auricular fibrillation, inversion (?) of T_2 and T_3 and preponderance of the right ventricle

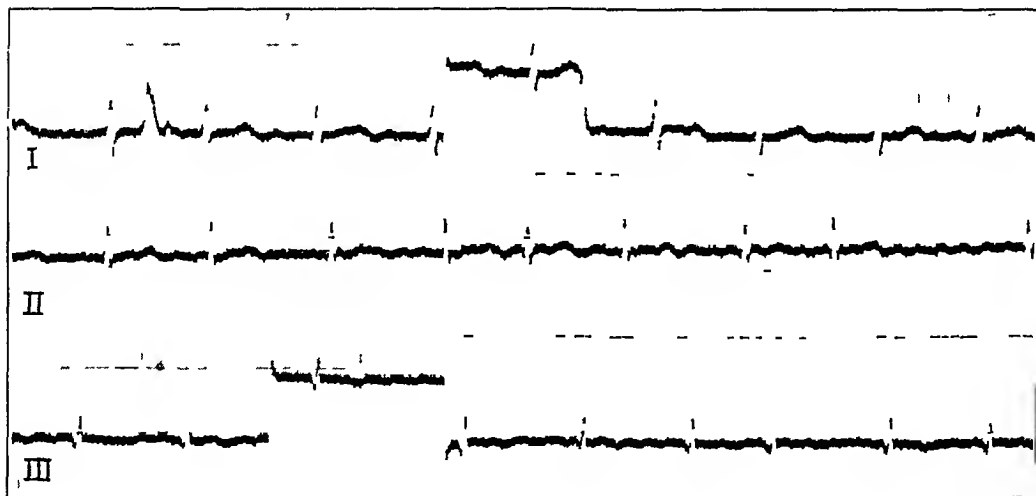


Fig 5—Dec 30, 1927 There were auricular fibrillation, an auricular rate of 450, a ventricular rate of 90, an occasional left ventricular ectopic beat and a low amplitude of the ventricular complex

by many yellow plaques. Many of these had a stonelike consistency, and the free borders of the cusps were also thick and sclerotic. The aortic leaflet of the mitral valve presented the same type of changes, but these did not extend down to the line of closure. The cardiac valves had the following circumferences

aortic valve, 8.3 cm, mitral valve, 10.5 cm, pulmonary valve, 9.5 cm, and tricuspid valve, 15 cm. The left ventricle was not enlarged, and its wall measured up to 10 mm in thickness. The right ventricle was not enlarged, but the tricuspid valve seemed to be dilated, and its wall measured up to 5 mm in thickness. The line of demarcation between fat and muscles was not sharp. The right auricle was

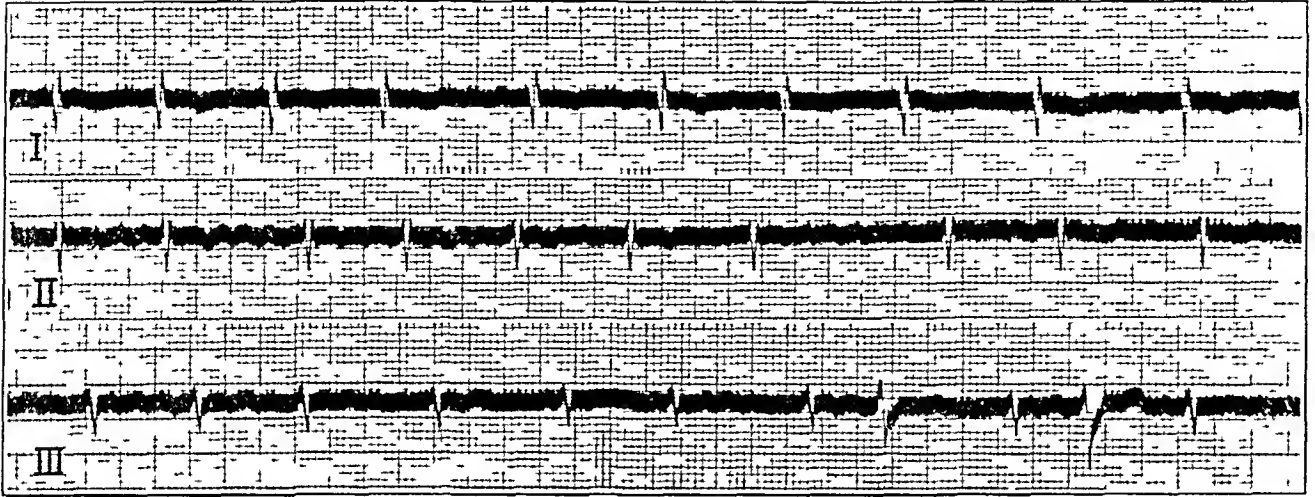


Fig 6—May 23, 1932. The findings were practically the same as those noted on Dec 30, 1927 (fig 5).



Fig 7—*A*, the right auricle and ventricle. Note the tremendous size of the auricle. *B*, the heart opened. *T* indicates tumor, *A*, auricle, *Tr*, tricuspid valve, and *V*, right ventricle. Note the tumor of the auricle and the size of the ventricle as compared with the size of the auricle.

markedly dilated, its wall measuring 4.6 mm in thickness. The pectinate muscles were hypertrophic. The aorta was covered by many yellow intimal plaques, and the mouth of the right coronary ostium was encroached on by some of these. The

coronary arteries were thick and cordlike, and the intima was covered by many yellow plaques that were often calcified. The first part of the anterior descending branch of the left coronary artery was markedly narrowed by these changes, but there was no complete occlusion.

Microscopic examination of the heart showed that most of the fibers stained irregularly in intensity. The paler fibers usually were lacking in nuclei and appeared hyalinized. Many of the fibers were fragmented along the lines of the intercalated disks. The larger vessels were markedly tortuous, and the lumens were narrowed by intimal proliferation. There was much newly formed connective tissue between the fibers of the cardiac muscle.

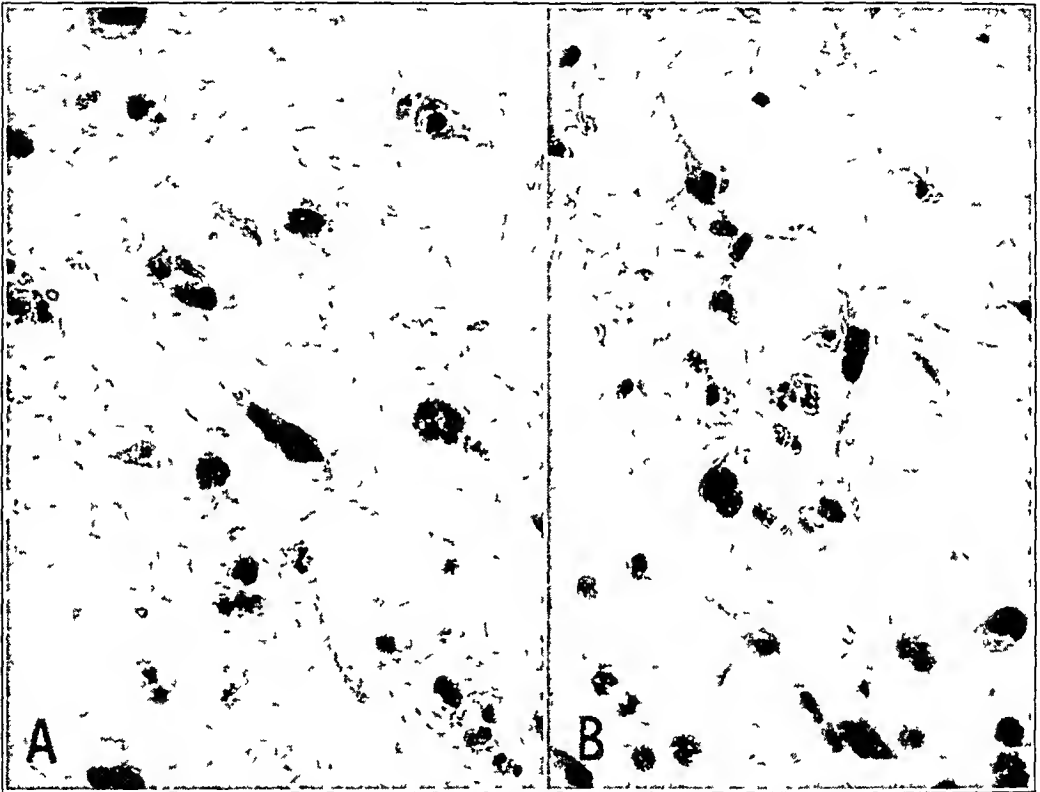


Fig 8—*A*, note the large amount of intercellular stroma and the oval cells with protoplasmic elongations. Hematoxylin and eosin preparation, $\times 400$. *B*, section of the tumor. Note the triangular cells and the large amount of intercellular stroma, $\times 300$.

The tumor of the heart, for the most part, showed in cross section an acellular material staining with various degrees of intensity, partly eosinophilic and partly basophilic. In a number of fields there were also cellular elements which were either oval or triangular, with processes extending in three directions, corresponding to the angles of the triangle. Also the oval cells had cytoplasmic elongations extending in two directions. Some of these cells were multinuclear. In some fields the eosinophilic material was slightly granular and occasionally vacuoles were present in this material as well as in the triangular cells. A number of well formed small and larger vessels were seen throughout the tumor. The periphery of the tumor, however, revealed tiny islets of vascular channels, sometimes incom-

pletely formed and lined with endothelial cells. In the periphery of the tumor there was also blood pigment, some of which was present in endothelial leukocytes and some free in the tissue. Sections which were stained with mucicarmine gave a positive reaction for mucin.

COMMENT

This paper records the history, physical findings and autopsy observations for a man aged 63 who had had "heart symptoms" for forty-three years. Death occurred from rupture of the colon. At the age of 20 the first symptoms of heart disease were noted. From that time until his death his life was a seesaw between periods of well-being and periods of illness. Serial roentgenograms and electrocardiograms are analyzed. At the age of 55 there were symptoms of angina pectoris. During the year preceding his death he had symptoms and signs of ulcerative colitis and, just before death, obstruction of the lower portion of the bowel, with perforation. The autopsy revealed, in summary, myxoma of the right auricle, high grade coronary and aortic sclerosis, ulcerative colitis with rupture and carcinoma of the rectum.

This story represents the longest case history on record of a tumor of the heart—forty-three years. The arteriosclerosis observed at autopsy gave symptoms only during the last seven or eight years of life and certainly represented a later development than the cardiac tumor. There is no way of ascertaining whether the myxoma was congenital or acquired. The early history suggests a strong possibility of a cardiac lesion in youth. The progressive increase in the size of the heart was probably due to a gradual increase in the size of the tumor. The electrocardiograms point strongly to the increasing amount of work done by the right auricle, with final cardiac exhaustion. During the later years of life, the heart was progressively unable to carry on its work, even when the activities of the patient were considerably reduced. Although death finally occurred from causes extraneous to the heart, the patient's cardiac mechanism was definitely showing signs of increasing inefficiency.

The diagnosis of benign tumor of the heart was not made during life. There are several outstanding features of the case which in retrospect seem to have greater importance than was attached to them during the life of the patient. The absence of a history of rheumatic involvement, the long duration of the illness, the long periods of well-being which intervened between attacks of congestive failure and the change in the character of the murmur are suggestive. The roentgen findings of a marked increase in the size of the right side of the heart, the absence of any electrocardiographic signs of preponderance of the left ventricle, the early presence of a high, notched P wave, the onset of auricular fibrillation and the constantly enlarging liver should have

directed our attention more forcibly to the right auricle. There were never any signs of thyrotoxicosis, nor was the picture ever typically that of the usual valvular diseases of the heart.

Previous investigators have emphasized the changeability of the murmur heard in cases of cardiac tumor. It will be recalled that Dr. Hamburger's notes reported such a variation during the earlier periods of this patient's life.

It is true that benign tumors of the heart are exceedingly rare and that none has been diagnosed ante mortem. An increasing number of reports on tumor of the heart are appearing in the literature, and it seems possible that, as has happened frequently with other rare conditions, consciousness of the anomaly may lead to more frequent diagnosis. Up to 1930 in only 1 case of metastatic tumor had the diagnosis been made ante mortem. Nine more cases were added in the next seven years. In 2 cases of primary malignant tumor the diagnosis was made ante mortem (in 1934 and 1935, respectively). It is hoped that this story may add to the possibility of the early diagnosis of primary benign tumor.

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BLOOD IN THROMBOANGIITIS OBLITERANS

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Beinhard,¹ in a study of 15 cases of thromboangitis obliterans, found that the values for the calcium content of the serum and for the cholesterol, the chlorides and the carbon dioxide-combining power of the plasma were within normal limits. Three types of dextrose tolerance curves were found, but only 3 of the 15 patients appeared to have a diminished tolerance for dextrose. Heitz² studied 27 cases of "obliterating arteritis". Only 2 of these appeared to be characteristic examples of thromboangitis obliterans (cases 12 and 13). The values for the cholesterol in these cases were 217 and 348 mg per hundred cubic centimeters of plasma, respectively. Ssokoloff³ found normal values for cholesterol in cases of "spontaneous gangrene" of the extremities.

Silbert, Kornzweig and Friedlander,⁴ in a study of 69 cases of typical thromboangitis obliterans, found an average volume of the whole blood of 643 cc for each kilogram of body weight, this was an average reduction of 21 per cent in the value for normal persons, which is 827 cc for each kilogram of body weight. The value for the hemoglobin in these 69 cases appeared to be greater than normal. As a result of these findings the authors drew the tentative conclusion that the blood is usually concentrated in thromboangitis obliterans. In about 10 per cent of the cases the volume of blood was normal. However, the patients were exercised in order to insure a proper distribution of the dye in

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1 Bernhard, A. Summary of the Chemical Blood Findings in Thromboangitis Obliterans, *M Rec* **97** 430-431 (March 13) 1920

2 Heitz, J. De la cholestérinémie chez les sujets affectés d'artères oblitères, *Ann de med* **14** 378-409 (Nov) 1923

3 Ssokoloff, N. A. Ueber den Cholesteringehalt des Blutes bei Spontangangan der Extremitäten vor und nach der eiseitigen Epinephrektomie, *Deutsches Arch f klin Med* **144** 202-206 (June) 1924

4 Silbert, S., Kornzweig, A. L., and Friedlander, M. Thrombo-Angitis Obliterans (Buerger). IV. Reduction of Blood Volume, *Arch Int Med* **45** 948-957 (June) 1930

the body for the determination of the blood volume, a procedure which is not ordinarily used. Moreover, in the determination of the hematocrit value, 0.1 cc of 20 per cent solution of potassium oxalate was used, which may have decreased the hematocrit values, as it has been shown that when dry potassium oxalate is used the volume of the erythrocytes is about 3 per cent less than when a dilute solution of potassium oxalate is used and correction is made in the final reading. No valid criticism can be offered of those two variations in technic, since they were apparently used in the study of both normal persons and patients with thromboangitis obliterans.

Horton and Brown⁵ reported 1 case in which thromboangitis obliterans was associated with polycythaemia vera. This was the first case of the two diseases observed at the Mayo Clinic up to that time. Norman and Allen,⁶ in a study of 98 cases of polycythaemia vera, did not find any instance of thromboangitis obliterans. In a study of 35 cases of "relative polycythemia" they reported 5 instances of thromboangitis obliterans. The hematocrit values varied from 51 to 63 per cent, and the blood volume varied from 63 to 88 cc for each kilogram of body weight. Friedlander and Silbert,⁷ in a study of 40 cases of thromboangitis obliterans, found increases in the total ash content, in the values for the total protein and calcium in the serum and in the value for the cholesterol in the plasma. No striking abnormalities were found in the values for the chlorides in the plasma and for the sugar in the blood, and the results of tests for tolerance for sugar were normal. These authors expressed the opinion that there is a tendency toward concentration of the blood in thromboangitis obliterans. Silbert and Friedlander⁸ showed subsequently that the administration of thyroid increased the blood volume from 25 per cent below normal to normal levels in cases of thromboangitis obliterans. On cessation of administration of thyroid the value for the blood volume returned to the original level. Subsequently, Friedlander, Laskey and Silbert⁹ observed 25 patients who had undergone bilateral oophorectomy. These patients

5 Horton, B. T., and Brown, G. E. Unusual Cases of Thrombo-Angitis Obliterans. Their Association with Polycythemia Vera and Traumatic Myelitis, *M. Clin. North America* **12** 1617-1627 (May) 1929.

6 Norman, I. L., and Allen, E. V. The Vascular Complications of Polycythemia, *Am. Heart J.* **13** 257-274 (March) 1937.

7 Friedlander, M., and Silbert, S. Thrombo-Angitis Obliterans (Buerger) VI. Chemistry of the Blood, *Arch. Int. Med.* **48** 500-506 (Sept.) 1931.

8 Silbert, S., and Friedlander, M. Studies in Thrombo-Angitis Obliterans (Buerger) VIII. Effect of Thyroid Administration on Blood Volume in Thrombo-Angitis Obliterans, *J. A. M. A.* **97** 17-18 (July 4) 1931.

9 Friedlander, M., Laskey, N., and Silbert, S. Reduction of Blood Volume Following Bilateral Oophorectomy, *Proc. Soc. Exper. Biol. & Med.* **30** 1263-1264 (June) 1933.

were found to have an average blood volume that was 25 per cent less than normal. Coincident with this there was an increase in the amount of cholesterol and fibrinogen in the blood plasma. They concluded that the ovaries produce some substance capable of influencing the blood volume. Rabinowitz and Kahn¹⁰ found that the normal value for the phospholipids was 203 mg for each hundred cubic centimeters of plasma and that the value in cases of thromboangitis obliterans was 236 mg per hundred cubic centimeters of plasma.

MATERIAL STUDIED

A study was made of the various components of the blood of 105 patients with thromboangitis obliterans observed at the clinic, 76 of the patients were gentiles and 29 were Jews. The studies were made only for patients who showed characteristic symptoms and clinical manifestations of thromboangitis obliterans. Patients who apparently had mixed arterial lesions, both degenerative and inflammatory, and those whose arterial lesions were solely arteriosclerotic were excluded from this study.

METHODS OF STUDY

The blood volume was determined by means of the Rowntree, Brown and Roth¹¹ modification of the Keith, Rowntree and Geraghty¹² method. All the determinations in this study as well as those reported in the monograph by Rowntree, Brown and Roth were made by one person (Dr. Roth), who has made approximately one thousand determinations. The value for the calcium in the serum was determined by the Clark-Collip¹³ modification of the Kramer-Tisdall¹⁴ method, the value for the blood urea, by the method of Van Slyke and Cullen,¹⁵ the value for the inorganic phosphorus in the serum, by the method of Fiske and Subbarow,¹⁶ the values for cholesterol and total fats in the plasma, by the methods of Bloor,¹⁷

10 Rabinowitz, H. M., and Kahn, J. Relationship of Phospholipin Metabolism to Thromboangitis Obliterans and Its Treatment, *Am J Surg* **31** 329-339 (Feb) 1936

11 Rowntree, L. G., Brown, G. E., and Roth, G. M. *The Volume of the Blood and Plasma*, Philadelphia, W. B. Saunders Company, 1929

12 Keith, N. M., Rowntree, L. G., and Geraghty, F. J. A Method for the Determination of Plasma and Blood Volume, *Arch Int Med* **16** 547-576 (Oct) 1915

13 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for Determination of Blood Serum Calcium, with a Suggested Modification, *J Biol Chem* **63** 461-464 (Jan) 1925

14 Kramer, B., and Tisdall, F. F. A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, *J Biol Chem* **47** 475-481 (June) 1921

15 Van Slyke, D. D., and Cullen, G. E. A Permanent Preparation of Urease, and Its Use in the Determination of Urea, *J Biol Chem* **19** 211-228 (July) 1914

16 Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J Biol Chem* **66** 375-400 (Dec) 1925

17 Bloor, W. R. The Determination of Cholesterol in Blood, *J Biol Chem* **24** 227-231 (March) 1916, The Determination of Small Amounts of Lipid in Blood Plasma, *ibid* **77** 53-73 (April) 1928

and the value for lecithin in the plasma, by the method of Whitehorn¹⁸ The value for the serum protein was determined by the macromethod of Kjeldahl

RESULTS

Blood Volume—The total volume of whole blood was determined for 55 patients 40 gentiles and 15 Jews In 2 cases a limb had been amputated For the entire group the volume of blood varied from 4,305 to 7,113 cc , and for each kilogram of body weight it varied from 59 to 109 cc The respective averages were 5,541 and 80.2 cc The blood volume of the Jews varied from 4,305 to 7,113 cc , and for each kilogram of body weight it varied from 59 to 97 cc The respective averages were 5,234 and 74.1 cc The blood volume of the gentiles varied from 4,420 to 6,645 cc , and for each kilogram of body weight it varied from 61 to 109 cc The respective averages were 5,670 and 82.8 cc (table 1)

TABLE 1—Average Hematocrit Value and Blood Volume in Thromboangitis Obliterans

No of Cases	Race	Weight, Kg	Height, Cm	Hematocrit Value, per Cent	Blood			Plasma		
					Vol ume, Cc	Cc per Kg	Cc per Sq M	Vol ume, Cc	Cc per Kg	Cc per Sq M
55	Gentiles and Jews	66.8	70.2	46.5	5,541	80.2	3,053	2,941.0	42.8	1,642.0
40	Gentiles	67.8	69.2	46.7	5,670	82.8	3,155	2,995.9	44.0	1,665.0
15	Jews	65.0	72.6	46.1	5,234	74.1	2,950	2,810.0	39.9	1,586.8

In contrast with these figures are the values for the total blood volume when this same group of patients, irrespective of nationality, was divided into three groups according to body build The first group included the patients who were overweight, the second group included those who were of standard weight and the third group included those who were underweight Classification of these groups was made as follows The patients who were considered of standard weight were those whose weight, taking into consideration sex, height and age, varied less than 10 per cent from the actuarial figures commonly in use The patients who were underweight and overweight were those whose weights varied more than 10 per cent from the actuarial figures The blood volume of the underweight patients varied from 4,305 to 6,394 cc , and for each kilogram of body weight it varied from 69 to 109 cc The respective averages were 5,331 and 91 cc (table 2) The blood volume of the patients of normal weight varied from 4,035 to 6,850 cc , and for each kilogram of body weight it varied from 59 to 101 cc The

18 Whitehorn, J. C. A Method for the Determination of Lipoid Phosphorus in Blood and Plasma, J Biol Chem 62 133-138 (Nov) 1924

respective averages were 5,496 and 786 cc (table 3) The blood volume of the patients who were overweight varied from 4,361 to 7,113 cc, and for each kilogram of body weight it varied from 54 to 84 cc

TABLE 2—Hematocrit Values and Blood Volume for Underweight Patients

Case	Age, Yr	Weight, Kg	Height, Cm	Hematocrit Value, per Cent	Blood			Plasma		
					Volume, Cc	Cc per Kg	Cc per Sq M	Volume, Cc	Cc per Kg	Cc per Sq M
1	44	61	68	47	6,062	99	3,590	3,233	53	1,890
2	45	56	66	48	5,118	91	3,160	2,660	48	1,610
3	42	63	66	41	5,895	94	3,388	3,478	55	1,999
4	30	65	71	45	5,545	85	3,047	3,050	47	1,676
5	44	57	70	44	5,282	93	3,107	2,958	52	1,740
6	43	60	67	46	4,873	81	2,901	2,632	44	1,367
7	34	46	66	58	5,660	109	3,605	2,375	46	1,513
8	45	66	70	44	4,560	69	2,519	2,326	35	1,285
9	37	61	67	50	4,654	78	2,738	2,327	38	1,369
10	49	60	69	43	5,470	91	3,199	3,115	43	1,822
11	29	57	68	36	5,800	102	3,473	3,715	65	2,225
12	38	63	68	53	6,394	102	3,675	3,005	48	1,727
13	46	77	64	46	6,092	105	3,808	3,290	57	2,056
14	38	57	68	45	4,670	82	2,800	2,565	45	1,535
15	25	54	66	47	4,920	91	3,075	2,605	48	1,627
16	29	50	63	43	4,305	86	2,851	2,454	49	1,625
Average 38.6					5,331	91.1	3,183	2,862	48.3	1,704

TABLE 3—Hematocrit Values and Blood Volume of Patients of Normal Weight

Case	Age, Yr	Weight, Kg	Height, Cm	Hematocrit Value, per Cent	Blood			Plasma		
					Volume, Cc	Cc per Kg	Cc per Sq M	Volume, Cc	Cc per Kg	Cc per Sq M
1	51	75	68	46	5,960	79	3,185	3,215	43	1,718
2	38	65	64	43	4,420	67	2,600	2,500	39	1,470
3	41	83	69	46	5,929	71	3,060	3,197	39	1,620
4	43	69	66	48	5,005	73	2,796	2,603	38	1,454
5	39	70	68	42	5,754	82	3,162	3,337	48	1,833
6	42	90	72	44	6,201	69	2,925	3,477	39	1,640
7	35	73	68	43	5,763	79	3,115	3,285	43	1,776
8	35	65	69	42	5,930	91	3,350	3,435	53	1,941
9	44	71	69	49	6,205	88	3,409	3,170	45	1,741
10	24	68	67	50	5,394	70	2,932	2,697	40	1,466
11	35	69	66	51	4,996	71	2,823	2,448	35	1,383
12	40	59	63	51	5,413	92	3,426	2,652	45	1,678
13	53	70	60	57	5,114	73	3,080	2,199	31	1,325
14	27	58	66	49	5,100	88	3,091	2,599	46	1,575
15	47	80	71	42	5,840	73	2,935	3,385	42	1,701
16	35	78	68	51	6,645	86	3,500	3,265	43	1,715
17	23	68	70	44	6,850	101	3,723	3,840	56	2,087
18	54	71	64	41	5,001	70	2,825	2,950	42	1,667
19	25	59	64	47	4,422	75	2,730	2,345	40	1,448
20	39	70	63	44	4,035	59	2,970	2,219	32	1,661
21	49	66	66	47	4,840	73	2,813	2,565	40	1,491
22	47	76	67	45	5,310	70	2,855	2,920	38	1,570
23	53	65	63	51	5,750	88	3,464	2,820	44	1,699
24	47	62	56	50	6,020	97	3,562	3,010	49	1,781
Average 40.3					5,496	78.6	3,097	2,922	42.1	1,643

The respective averages were 5,857 and 706 cc The hematocrit values of the entire group studied varied from 40 to 58 per cent, the average was 46.5 per cent (table 1) There was no significant difference in the values for Jews and gentiles (46.1 and 46.7 per cent, respectively, table 1) or for the subjects who were of normal weight, overweight or underweight (46.8, 46.6 and 46 per cent, respectively, tables 2 to 4)

Serum Calcium—The values for serum calcium were determined for 55 patients, 41 gentiles and 14 Jews. The average ages of the gentiles and of the Jews were 37.8 and 39.2 years, respectively. No significant variation from normal was found (table 5).

Inorganic Phosphorus—The values for inorganic phosphorus were determined for 50 patients, 38 gentiles and 12 Jews. The average ages

TABLE 4—*Hematocrit Value and Blood Volume of Overweight Patients*

Case	Age, yr	Weight, kg	Height, Cm	Hemato- crit Value, per Cent	Blood			Plasma		
					Volume, Cc	Cc per Kg	Cc per Sq M	Volume, Cc	Cc per kg	Cc per Sq M
1	48	77	64	51	5,470	71	3,020	2,680	35	1,480
2	34	77	76	47	6,075	79	2,975	3,220	42	1,576
3	34	82	69	45	5,305	65	2,693	2,920	36	1,480
4	43	77	67	44	6,441	84	3,447	3,607	47	1,915
5	51	79	67	50	5,950	76	3,132	2,975	38	1,566
6	42	84	62	51	6,919	82	3,740	2,542	41	1,374
7	42	91	69	47	5,562	61	2,710	2,948	32	1,436
8	44	78	67	40	5,810	75	3,053	3,455	44	1,834
9	49	96	69	48	6,280	66	2,845	3,265	34	1,502
10	35	77	66	47	5,996	78	3,220	3,178	41	1,707
11	44	81	68	48	4,361	54	2,260	2,268	28	1,175
12	35	79	64	43	5,270	67	2,849	2,995	38	1,619
13	52	78	66	48	5,450	70	2,914	2,830	36	1,513
14	44	120	67	44	7,113	60	3,161	3,983	34	1,770
Average 42.7		84	67.2	46.6	5,857	70.6	3,002	3,064	37.6	1,568

TABLE 5—*Values for Calcium, Inorganic Phosphorus, Cholesterol, Lecithin, Fatty Acids and Total Lipoids in Thromboangitis Obliterans*

Patients	Calcium, Mg per 100 Cc of Serum		Inorganic Phosphorus, Mg per 100 Cc of Serum		Lipoids, Mg per 100 Cc of Plasma							
					Cholesterol		Lecithin		Fatty Acids		Total Lipoids	
	Aver age	Range	Aver age	Range	Aver age	Range	Aver age	Range	Aver age	Range	Aver age	Range
Total	10.3	8.8-11.7	3.5	2.5-4.5	192.4	102-273	244.0	182-365	377.5	194-603	563.8	360-871
Gentiles	10.1	8.8-11.6	3.4	2.5-4.4	184.4	102-273	236.0	182-312	371.6	194-603	549.8	360-871
Jews	10.8	9.7-11.7	3.6	2.5-4.5	215.6	133-273	274.6	203-365	395.3	230-497	605.6	413-770

of the two groups of patients were 37.8 and 39.2 years, respectively. No significant variations from normal were found (table 5).

Lipoids—The values for the plasma cholesterol were determined for 43 patients, 32 gentiles and 11 Jews (table 5). The concentration of lecithin in the blood plasma was determined for 24 patients, 19 gentiles and 5 Jews (table 5). The values for the fatty acids and total lipoids in the blood plasma were determined for 36 patients, 27 gentiles and 9 Jews (table 5). The average ages of the patients in the two groups were 37.4 and 40.8 years, respectively.

Blood Urea—The concentration of urea in the blood was determined in 40 cases. The average value was 26.9 mg per hundred cubic

centimeters of blood, and the values ranged from 14 to 46 mg per hundred cubic centimeters. These values are considered normal.

Serum Protein—The values for the serum protein were determined in 12 cases. The average value was 6.4 Gm per hundred cubic centimeters, and the values ranged from 5 to 8.7 Gm per hundred cubic centimeters. These are considered normal values.

COMMENT

Our studies indicate that the values for the blood urea, serum calcium, protein and inorganic phosphorus are normal in cases of thromboangitis obliterans. The average hematocrit value (46.5 per cent) in 54 cases was near the upper limits of normal, but the hematocrit value exceeded 50 per cent in only 9 instances. In a study of 49 normal men of various body build, Rowntree, Brown and Roth found that the hematocrit value varied from 36 to 47 per cent, the average was 42 per cent. However, Haden¹⁹ said that a normal erythrocyte count of 5,000,000 per cubic millimeter of blood gives a hematocrit value of 48 per cent. The difficulty in evaluating the significance of our figures is chiefly one of accepting a normal value for purposes of comparison. Certainly, many of the values determined can be accepted as normal, and the significance of those which seem somewhat greater than normal can be challenged chiefly because they lie so close to the normal range. One conclusion seems entirely warranted, namely, there are no characteristic changes in the hematocrit value in cases of thromboangitis obliterans.

The average value which we have found for the blood volume for each kilogram of body weight (91.1 cc) for patients who were underweight agrees with the average figure (92 cc) determined for underweight patients by Rowntree, Brown and Roth. However, a variation in the value for patients of normal weight (78.6 cc for each kilogram of body weight) is less than that (89.1 cc for each kilogram of body weight) found for patients of similar body build by Rowntree, Brown and Roth. Moreover, the values obtained in our studies of this group were less than the average values found by Rowntree, Brown and Roth for 20 of the 24 patients. This finding seems perhaps more significant when one considers that the average weight of our group of patients (70 Kg) was about the same as that of the normal persons (69.1 Kg) studied by Rowntree, Brown and Roth. The average values for the blood volume of the overweight patients in our cases was 70.6 cc per kilogram of body weight, the value for patients of similar body build who were studied by Rowntree, Brown and Roth was 81.8 cc. In 12 of our 14 patients in this group the value was less than the average.

¹⁹ Haden, R. L. Accurate Criteria for Differentiating Anemias, *Arch Int Med* 31:766-780 (May) 1923.

determined by Rowntree, Brown and Roth. However, the average weight for our group (84 Kg) was substantially greater than that of the patients studied by Rowntree, Brown and Roth, which was 77.6 Kg.

It is apparent that no far reaching conclusions may be drawn from these studies, for the blood volume of underweight patients who have thromboangitis obliterans appears normal while that of patients of normal weight and those who are overweight appears to be decreased. Certainly, the conclusion advanced by Friedlander and Silbert, that the blood seems to be concentrated in thromboangitis obliterans, seems on a none too secure basis. Since thromboangitis obliterans causes occlusion of arteries and veins, the explanation for a decrease in the blood volume in many cases may lie in the diminished volume of the vascular tree rather than in concentration of the blood. Silbert, Kornzweig and Friedlander considered this possibility and apparently eliminated it by finding normal blood volumes in cases in which occlusive arterial disease was the result of arteriosclerosis. However, it must be kept in mind that veins are not occluded in arteriosclerotic disease but that they may be occluded in thromboangitis obliterans. It is well known from anatomic and arteriographic studies (Allen and Barker²⁰) that the veins of the extremities occupy much more space than do the arteries and that a disease which occludes both arteries and veins might cause a discernible reduction in blood volume, while one which involves arteries alone might not do so. It is true, certainly, that many patients who have characteristic thromboangitis obliterans have a normal blood volume, this observation alone casts some doubt on the assumption that diminished blood volume is an integral part of thromboangitis obliterans.

Studies of the concentration of cholesterol in the plasma of normal persons have demonstrated a great variation and a wide range. Denis,²¹ Bloor,²² Bruger and Poindexter,²³ McGee,²⁴ Boyd²⁵ and Page and his

20 Allen, E. V., and Barker, N. M. Roentgenologic Visualization of the Veins of the Extremities. Preliminary Description of a Method, Proc. Staff Meet., Mayo Clin **9** 71-74 (Jan 31) 1934.

21 Denis, W. Cholesterol in Human Blood Under Pathological Conditions, J Biol Chem **29** 93-110 (Feb) 1917.

22 Bloor, W. R. The Distribution of the Lipoids ("Fat") in Human Blood, J Biol Chem **25** 577-599 (July) 1916.

23 Bruger, M., and Poindexter, C. A. Relation of Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteo-Arthritis and Arteriosclerosis), Arch Int Med **53** 423-434 (March) 1934.

24 McGee, L. Blood Cholesterol in Disturbances of Basal Metabolic Rate, Ann Int Med **9** 728-738 (Dec) 1935.

25 Boyd, E. M. A Differential Lipid Analysis of Blood Plasma in Normal Young Women by Micro-Oxidative Methods, J Biol Chem **101** 323-336 (June) 1933.

co-workers²⁶ found that the range of normal values was 150 to 260 mg per hundred cubic centimeters. Page, Kirk, Lewis, Thompson and Van Slyke,²⁷ who used a gasometric method of determination, found a mean value of 232 mg per hundred cubic centimeters. Bruger and Poindexter indicated that the range between 230 and 250 mg is suggestive of hypercholesteremia. In a study of 32 normal persons we found that the average value was 180.8 mg per hundred cubic centimeters and that the range was from 135 to 262 mg per hundred cubic centimeters. In only 2 of the 43 cases of thromboangitis obliterans which we studied did the values for cholesterol exceed the highest values found in our study of normal persons. De Langen²⁸ reported a series of observations made for natives of Java, China, Japan and India. The cholesterol content of the blood of these natives was found to average 40 to 50 per cent less than that of the blood of Europeans. This corresponded closely with the diet of the natives, which is poor in cholesterol, a customary feature in their respective countries. Bloor²⁹ also said that the greatest single factor influencing the concentration of the lipids in the plasma appears to be diet, particularly the amount of fat which the food contains.

The question arose as to whether there is any great difference in the diet of gentiles and Jews, and if so, whether it is sufficient to produce a significant increase in the cholesterol content of the plasma. Whereas in our study of patients with thromboangitis obliterans the average value for the cholesterol in the plasma of Jews was 31.2 mg per hundred cubic centimeters higher than that of the gentiles, the values were still within normal limits. Hypercholesteremia has been reported to be associated with obesity, however, in most instances the obesity was complicated by some degenerative disease. In other instances normal values have been reported for cholesterol. Bruger and Poindexter in 11 per cent of 53 cases of uncomplicated obesity found that the value for cholesterol was more than 250 mg per hundred cubic centimeters of plasma. McGee observed normal values in 20 cases of obesity. In our group of cases in which thromboangitis obliterans was associated with obesity, the average value for cholesterol was 180 mg per hundred cubic centimeters of plasma, the values ranged from 102 to 273 mg

26 Page, I. H., Pasternack, L., and Burt, M. L. Ueber den Transport von Fetten und Lipoiden durch Blut nach Oeleingabe, *Biochem Ztschr* **223** 445-456, 1930.

27 Page, I. H., Kirk, E., Lewis, W. H., Jr., Thompson, W. R., and Van Slyke, D. D. Plasma Lipids of Normal Men at Different Ages, *J Biol Chem* **111** 613-639 (Nov.) 1935.

28 de Langen, C. D. Échanges cholesteriniques et pathologie de la race, *Presse méd* **24** 332-333 (July 27) 1916.

29 Bloor, W. R. Diet and the Blood Lipids, *Proc Soc Exper Biol & Med* **28** 701-702 (Feb.) 1931.

per hundred cubic centimeters Obesity apparently did not influence the cholesterol values

In our cases of thromboangitis obliterans the average value for lecithin per hundred cubic centimeters of plasma was 38.6 mg higher for the Jewish patients than it was for the gentiles, but the average values for both groups of patients were within normal limits

Page and his co-workers reported that the average value for fatty acids in the plasma of normal persons was 360.1 mg per hundred cubic centimeters and that the values ranged from 234.1 to 490.7 mg per hundred cubic centimeters Man and Gildea³⁰ reported an average value of 363.8 mg per hundred cubic centimeters but a slightly higher range of 287.6 to 451 mg per hundred cubic centimeters In our study of patients with thromboangitis obliterans we found that the average value for fatty acids for Jewish patients was 23.7 mg per hundred cubic centimeters of plasma higher than it was for gentile patients In our study of 36 patients with thromboangitis obliterans, a value for fatty acids in excess of that given as the upper normal limit by Man and Gildea was found in only 9 cases The average value of 37.7 mg per hundred cubic centimeters obtained in our study is slightly in excess of the average of 36.0 mg found by Page and his co-workers and the average of 36.3 mg found by Man and Gildea in a study of normal persons

Valuation of our studies of the cholesterol and fatty acids in the plasma in cases of thromboangitis obliterans is handicapped by the uncertainty as to what constitutes normal values and also by the wide range of normal values Certainly, our figures vary little from the values considered normal, and while in some instances our values definitely exceed those given for normal persons, in most instances they lie well within the accepted normal range Since this is true, we can say unequivocally that there is no characteristic change in the concentration of cholesterol or fatty acids in the plasma of patients with thromboangitis obliterans

SUMMARY

The values for serum calcium, serum protein, blood urea, serum lecithin and serum phosphorus were found to be within normal limits in our study of the blood in cases of thromboangitis obliterans In most instances the blood volume, hematocrit value and concentration of fatty acids and cholesterol in the plasma were found to be normal In some instances the blood volume was slightly decreased, and the hematocrit value and the concentration of fatty acids and cholesterol in the plasma were slightly increased We doubt the significance of these findings, since they are inconstant findings in thromboangitis obliterans

³⁰ Man, E. B., and Gildea, E. F. The Effect of the Ingestion of a Large Amount of Fat and of a Balanced Meal on the Blood Lipids of Normal Man, *J Biol Chem* 99:61-69 (Dec) 1932

BILATERAL CORTICAL NECROSIS OF THE KIDNEYS

REPORT OF THREE CASES

CURTIS F GARVIN, M D

AND

NORMAN VAN WEZEL, M D

CLEVELAND

The first description of bilateral cortical necrosis of the kidneys is accredited to Juhel-Renoy,¹ of France (1886). The condition is rare, the literature containing reports of about 70 cases. Reviews of the literature have been made by Scriver and Oertel² (1930), Ash³ (1933) and Evans and Gilbert⁴ (1936).

Bilateral cortical necrosis of the kidneys is so named because at autopsy both kidneys show more or less extensive necrosis of the cortex. Grossly the necrotic cortex is reddish yellow and soft, closely resembling a fresh infarct in appearance and consistency. However, the involved area does not have the shape of an infarct but has the shape of the cortex even to the point of involving the columns of Bertin. Only a thin layer of cortex adjacent to the capsule and the pyramids is spared. The necrosis is more or less patchy. The cortical vessels also are necrotic and contain thrombi, the composition, distribution, origin and significance of which are the cause of much debate. The liver usually shows cloudy swelling, in some cases, more especially those in which the condition is associated with dioxane poisoning, there is central necrosis of the liver.

The etiology of bilateral cortical necrosis of the kidneys has been the subject of much investigation. As far as can be determined, the condition affects previously normal kidneys. In the majority of cases there has been the complication of pregnancy, often associated with

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1 Juhel-Renoy, E. De l'anurie precoce scarlatineuse, *Arch gen de med* **17** 385-410, 1886

2 Scriver, W de M, and Oertel, H. Necrotic Sequestration of the Kidneys in Pregnancy (Symmetrical Cortical Necrosis). Clinical and Anatomic-Pathogenetic Study, *J Path & Bact* **33** 1071-1094 (Oct) 1930

3 Ash, J E. Bilateral Cortical Necrosis of the Kidneys (Angioneurotic Anuria), *Am J M Sc* **185** 71-86 (Jan) 1933

4 Evans, N, and Gilbert E W. Symmetrical Cortical Necrosis of the Kidneys. Report of a Case *Am J Path* **12** 553-560 (July) 1936

antepartum hemorrhage In other instances the condition has been associated with infectious diseases, trauma, the intravenous use of camphor and dioxane poisoning In several cases no other disease has been demonstrable Persons from 13 to 65 years of age have been affected, the average age being 32 (Evans and Gilbert) ⁴

The pathogenesis of the condition is obscure It is generally agreed that there is a disturbance of the vascular supply of the cortex, but whether this is due to multiple emboli, pressure, thrombosis, arteritis, necrosis of vessels or vascular stasis is not settled

The clinical picture in cases of bilateral cortical necrosis of the kidneys is fairly characteristic As has been stated, the disease usually occurs in pregnant women, most commonly during the latter part of pregnancy In a lesser number of cases the disease affects males or nonpregnant females The onset is usually sudden The paramount symptom is anuria Of lesser diagnostic import are headache, nausea, vomiting and epigastric pain and occasionally edema and convulsions The urine, if any is passed, contains albumin and casts, and occasionally blood and pus The blood pressure usually remains normal but may go up or down There is retention in the blood of nitrogenous products

In the differential diagnosis, nephritis, renal infarction and bilateral ureteral occlusion are to be considered In nephritis the onset is more gradual, anuria is less common and the course is usually less dramatic Renal infarction is more likely to be accompanied by pain, the anuria is not so constant and there usually is evidence of associated cardiovascular disease Bilateral ureteral obstruction can be differentiated by careful urologic examination

Bilateral cortical necrosis is usually fatal However, a few cases of supposed bilateral involvement with recovery are reported The treatment usually consists of the intravenous administration of dextrose and the forcing of fluids

Three cases of bilateral cortical necrosis of the kidneys have been encountered at the Cleveland City Hospital in the past four years These cases are of particular interest because the condition was not associated with pregnancy and because in all 3 cases it was associated with severe central necrosis of the liver

REPORT OF CASES

CASE 1—G P, a 40 year old Hungarian laborer, entered the Cleveland City Hospital on July 20, 1933, with a complaint of pain in the stomach of two days' duration He stated that on July 18 (two days before entry) he drank an undetermined amount of "almond extract" A few hours later diffuse abdominal pain and complete anuria developed

Physical examination showed the patient to be seriously ill, the respiration was rapid and deep, and the temperature was normal The optic disks were edematous There were rales at the bases of both lungs An apical systolic murmur was

audible. The blood pressure was 132 systolic and 68 diastolic. The abdomen was diffusely tender, and the edge of the liver was palpable 5 cm below the costal margin.

By catheterization no urine was obtained. The value for urea nitrogen was 140 mg per hundred cubic centimeters of blood, the value for creatinine was 14.5 mg. The icteric index was 27. The carbon dioxide-combining power was 9 volumes per cent. The Wassermann reaction of the blood was 4 plus, the Kline test of the blood gave a negative reaction. The leukocytes numbered 14,500 per cubic millimeter. The red blood cell count and the hemoglobin value were normal.

The patient remained anuric, became progressively lethargic and died eighteen hours after admission to the hospital.

The clinical diagnosis was acute toxic hepatitis and acute toxic nephritis due to poisoning, with terminal bronchopneumonia.

The autopsy was performed two hours after death. The body was that of a well nourished man whose external features were not remarkable. There was no peripheral edema.

None of the body cavities contained an excess of fluid.

The lungs revealed bronchopneumonia, greatest in extent in the lower lobe of the right lung.

The liver weighed 2,600 Gm. Its edges were rounded and extended 4 cm below the costal margin in the midclavicular line on the right. The capsule was thin, smooth and glistening. The cut surface bulged, it was bloody and of uniform tan color and the architecture was obscured. Microscopic examination showed severe central necrosis, in the necrotic areas the cells had lost their normal architecture, the nuclei were pyknotic or absent, the cytoplasm was granular and the cells had the appearance of "ghosts" of hepatic parenchyma. The periphery of each lobule showed early parenchymatous degeneration. The prominent feature was the absence of any cellular reaction or of proliferation of bile ducts.

The kidneys were similar. They were enlarged, and the capsule stripped with ease, leaving a smooth surface that was mottled, the color varying from reddish gray to purplish red. The cortex and the pyramids were well demarcated. The former measured 6 mm and the latter 23 mm in thickness. The cortical striations were seen only in scattered areas. The intervening areas consisted of purplish red amorphous tissue, portions of which were yellowish white. There was a narrow hyperemic and hemorrhagic zone between the cortex and the pyramids. These same changes were more extensive in the columns of Bertin. The renal pelvis was not unusual.

Microscopic examination revealed a patchy distribution of cortical necrosis, each area resembling a bland infarct. Both the tubular and the glomerular structures showed complete degeneration and loss of structure. Between these areas of necrosis the cortex was not abnormal. About each area was evidence of moderate polymorphonuclear reaction. There was a zone of hemorrhage between the cortex and the pyramids. About half the arteries in the necrotic area showed necrosis of their walls and thrombosis.

The other organs were not abnormal.

CASE 2—J. M., a 53 year old housewife, was admitted to the Cleveland City Hospital on April 24, 1936. She was unconscious. Her relatives stated that she had been in good health until six days before entry when anuria and intractable nausea and vomiting developed. These symptoms were associated with continuous epigastric pain which radiated through to the back. The patient became

increasingly drowsy and finally comatose. She was said to have had hypertension for several years. She was a chronic alcoholic addict but had had no liquor for four days prior to the onset of her illness.

Examination showed the patient to be dying. The fundi showed slight vascular disease. The blood pressure was 160 systolic and 85 diastolic. The heart and lungs were normal. The edge of the liver was palpable 6 cm below the costal margin. The skin was not icteric.

Catheterization yielded 4 cc of urine. This was light amber and showed an alkaline reaction, it contained albumin of grade 3. Microscopically the uncentrifuged specimen showed 20 to 30 white blood cells and an occasional red blood cell per high power field. The benzidine test for blood in the urine gave a negative reaction. The stool was normal in appearance, it contained bile and gave a negative reaction with the benzidine test. Blood culture showed no growth. The value for urea nitrogen was 22.76 mg per hundred cubic centimeters of blood, the value for creatinine was 12.6 mg. The Kline and the Wassermann test of the blood both showed a 4 plus reaction.

The patient died forty-five minutes after admission to the hospital. The clinical diagnosis was uremia of undetermined origin.

The autopsy was performed eighteen hours after death. The body was that of a well developed woman whose external features were not remarkable. There was no peripheral edema.

The heart weighed 275 Gm. There was typical syphilitic aortic valvulitis with widening of the commissures. The aorta showed marked syphilitic aortitis throughout the thoracic portion. The intima was scarred, and there were several small aneurysms which bulged outward 2 to 3 mm. Microscopic examination revealed the characteristic perivascular plasma cell infiltration and increased vascularity of the media.

The liver weighed 1,600 Gm. The capsule was thin, smooth and glistening. Beneath the capsule were numerous small petechiae, which were most numerous over the anterior surface of the right lobe. The cut surface of the liver was a light tan and showed an occasional small hemorrhage. The architecture was obscured. Microscopic examination revealed severe central necrosis, as was seen in case 1. Again the absence of evidence of cellular reaction was noted.

The gallbladder contained two small calculi, but there was no obstruction of the ducts.

Each kidney weighed 175 Gm and measured 11.5 by 5.5 by 4 cm. The capsules contained small areas of yellow tissue and stripped with ease, leaving a smooth surface which showed dilated veins and patchy areas with a hemorrhagic appearance. There were other areas that were yellow, but these were not sharply demarcated from the surrounding renal tissue.

On the cut surface the pyramids were normal, but the cortex showed yellow areas and surrounding hyperemia and hemorrhage. The cortex was not thickened, measuring 6 mm. The changes involved the columns of Bertin. The pelvis was not remarkable. Microscopic examination revealed large areas of necrosis involving tubules and glomeruli and showing both hyperemia and hemorrhage. Surrounding these was evidence of moderate polymorphonuclear reaction. The areas between the necrotic portions were not abnormal. The arteries also showed necrosis of their walls and some thrombosis. This involved nearly all the arteries seen in the areas of necrosis.

CASE 3—J. B., a 24 year old man, entered the Cleveland City Hospital on May 21, 1937, with a complaint of vomiting. He had been in good health until five days before admission to the hospital, when generalized abdominal cramps

developed. The following day nausea and vomiting developed, and on one occasion he vomited some digested blood. The day before entry he passed a tarry stool. A little urine had been voided, but the exact amount was not known. The patient was a chronic alcoholic addict but supposedly had not had any liquor for several months.

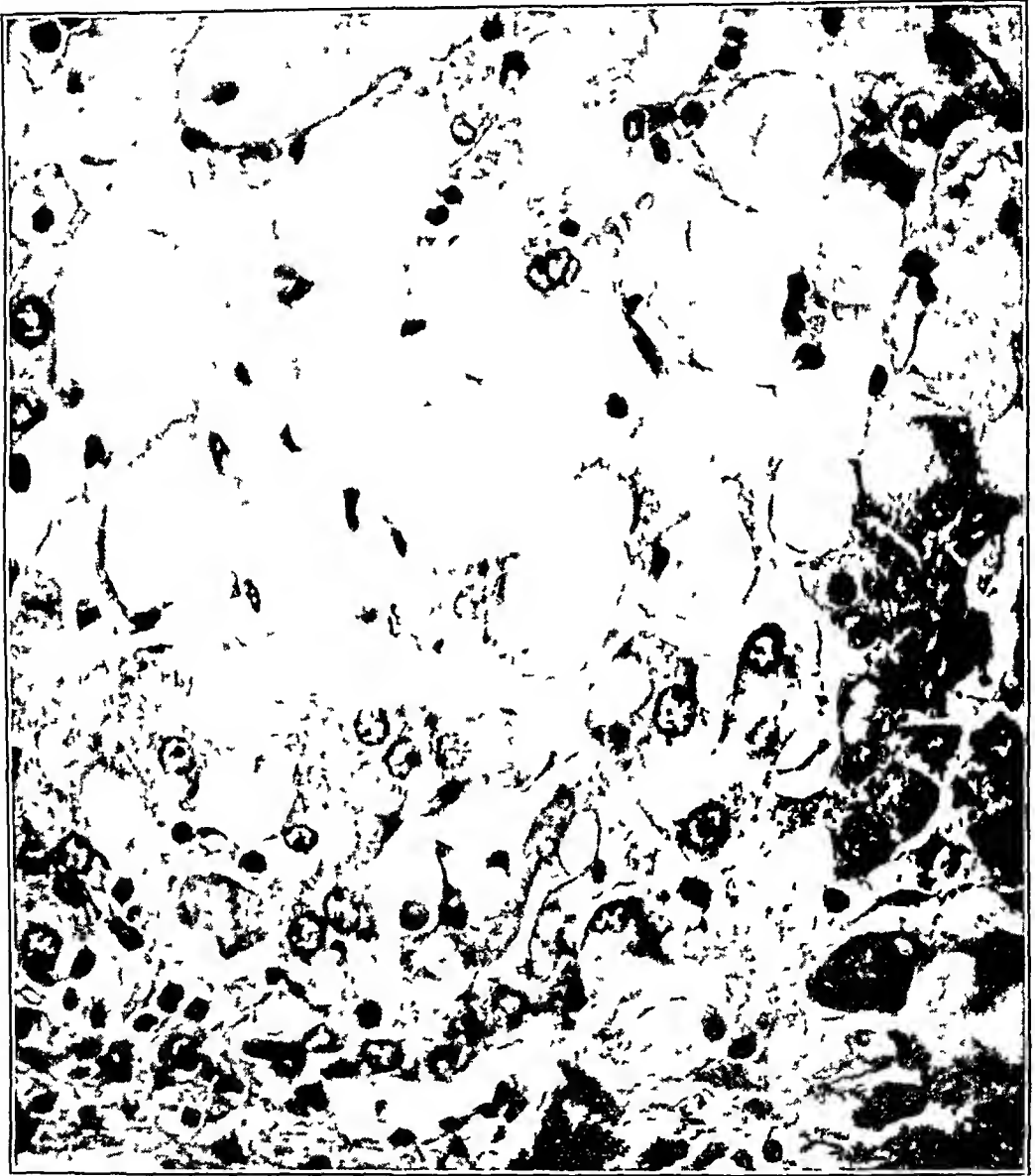


Fig 1 (case 3) —Central necrosis, the "ghost" appearance of the parenchymal cells and the early degenerative changes in the peripheral zones of the liver are shown. There is an absence of any evidence of cellular reaction, $\times 600$

Examination showed a well nourished, normally developed semicomatose man. He was obviously seriously ill. The optic disks were edematous. The lungs and heart were normal. The blood pressure was 160 systolic and 88 diastolic. The edge of the liver was palpable 5 cm below the costal margin. The skin was not icteric.

The leukocytes numbered 45,000 per cubic millimeter. Differential counts showed 95 per cent polymorphonuclear neutrophils and 5 per cent lymphocytes.

Catheterization yielded 2 cc of urine. Microscopically the uncentrifuged specimen showed a moderate number of granular and hyaline casts, occasional red blood cells and 20 to 30 white blood cells per high power field. The value for urea nitrogen was 246.1 mg per hundred cubic centimeters of blood, the value for creatinine was 14.5 mg. The reaction to the benzidine test for blood in the stools was 4 plus. The Kline test of the blood gave a negative reaction.

The patient rapidly became comatose, he remained anuric and died ten hours after admission to the hospital.



Fig 2 (case 3) —A cut surface of the kidney showing the irregular necrosis of the entire cortex extending into the columns of Bertin. The hemorrhagic zone sharply demarcates the cortex from the pyramids. The pelvic mucosa shows small hemorrhages.

The clinical diagnosis was uremia of undetermined origin.

The autopsy was performed five hours after death. The body was that of a well nourished man whose external features were not remarkable. There was no peripheral edema.

There was 500 cc of serous fluid in the peritoneal cavity but no pleural or pericardial effusion.

The lungs showed aspirated blood distributed in symmetric band-shaped zones throughout the subapical regions.

The liver weighed 2,250 Gm. The edges extended 5 cm below the costal margin in the midclavicular line and were rounded. The capsule was thin, smooth and glistening except for a few fibrous tags on the superior and anterior surfaces. The liver was moderately soft, and it cut with decreased resistance. The cut surface bulged but was not greasy or bloody. The central lobular areas were



Fig 3 (case 3)—Complete degeneration of a glomerulus and thrombosis of the afferent arteriole. The section also contains a normal glomerulus, $\times 350$

reddish brown and depressed, whereas the peripheral areas were grayish yellow and elevated. Microscopic examination revealed the same features as those seen in the first 2 cases, namely, severe central necrosis without evidence of cellular reaction (fig 1). Staining revealed the absence of both fat and glycogen in the areas of necrosis.

The kidneys were similar. Each weighed 200 Gm and measured 12 by 6 by 4.5 cm. The capsule was thickened, and it stripped with slight difficulty. Within

the capsule were dilated veins and small irregular hemorrhages. The surface of the kidney was smooth. The color varied, there were areas, irregular in shape, that were dark purple and hemorrhagic, surrounded by areas that were yellow and homogeneous. They were not sharply demarcated, and they faded into each other. The organ cut with the usual resistance, and the cut surface bulged considerably. The cortex and the pyramids were sharply demarcated, the former

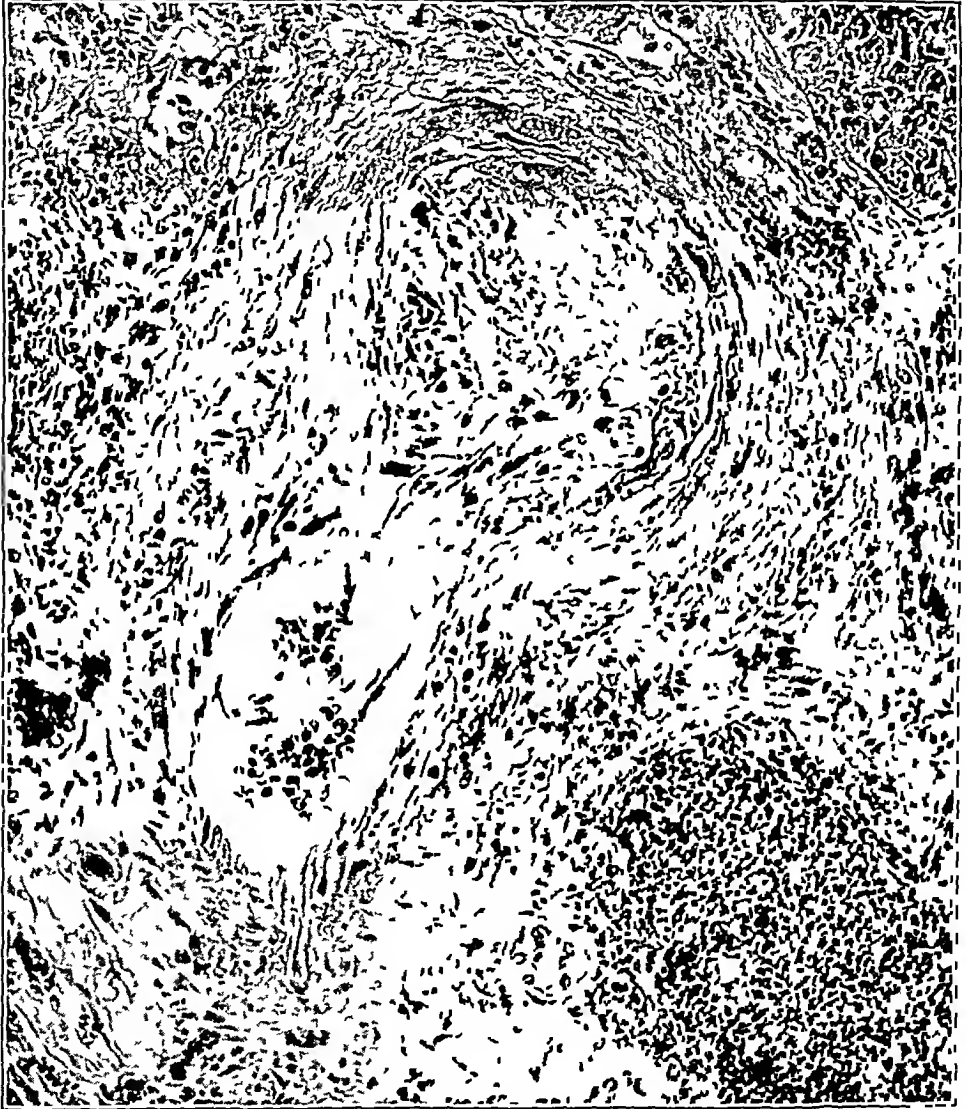


Fig 4 (case 3) —Necrosis of the wall and an organizing thrombus of a renal interlobular artery, $\times 250$

measured 6 mm in thickness and the latter 20 mm. This was accentuated by two factors: first, the light color of the cortex, which varied from tan to bright yellow, and, second, by the narrow, dark, hemorrhagic zone which followed the border of the cortex and the pyramids. The changes in the cortex involved the columns of Bertin and obscured the usual architecture. The changes in the cortex were not uniform. The yellow tissue was homogeneous, and the pinpoint areas representing glomeruli could not be made out. There were irregularly placed

patchy areas of hemorrhagic appearance. The zone of hemorrhage along the corticopyramidal border varied from 1 to 4 mm in thickness. The pyramids were not unusual. The pelvic mucosa showed numerous small hemorrhages (fig 2). Microscopic examination revealed small hemorrhages in the capsule with polymorphonuclear infiltration. This infiltration bordered the periphery of the cortex, both near the capsule and near the pyramids. The cortex itself showed complete loss of cellular structure, so that only the "ghosts" of the cells remained and involved both the glomeruli and the tubules (fig 3). There was a narrow zone near the pyramids wherein the glomeruli showed much less pathologic involvement, but they were few. In the zone of hemorrhage the arteries showed necrosis of their walls and conglutination of red blood cells in their lumens (fig 4). About half the arteries showed varying degrees of thrombosis. Staining revealed no fat or glycogen in the cortex.

The stomach showed the typical mosaic pattern consistent with chronic hypertrophic gastritis.

The gastrointestinal tract was filled with fresh clotted blood. Bleeding points were searched for carefully, and no explanation for the hemorrhage could be found.

The brain showed slight cerebral edema.

The other organs were essentially normal.

SUMMARY

The pathology, etiology and clinical features of bilateral cortical necrosis of the kidneys are discussed briefly.

Three cases of bilateral cortical necrosis of the kidneys in which autopsy was performed are reported.

These cases are of particular interest because the condition was not associated with pregnancy and because it was associated with central necrosis of the liver.

Central necrosis of the liver associated with bilateral cortical necrosis of the kidneys has been described especially in cases of dioxane poisoning. In the cases reported the condition may have been due to dioxane poisoning, but there was no proof of this, hence, the etiologic factor in these cases is unknown.

Dr Howard T. Karsner, Professor of Pathology, Western Reserve University, assisted in preparing the photomicrographs and criticized the manuscript.

INSULIN RESISTANCE

REPORT OF A CASE OF MARKED INSENSITIVENESS OF LONG
DURATION WITHOUT DEMONSTRABLE CAUSE

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Since July 1935 my colleagues and I have had the opportunity of observing a diabetic patient with crippling although afebrile rheumatoid arthritis who has required from 240 to 675 units of insulin daily for control of hyperglycemia and glycosuria. The situation is so extraordinary that certain special studies have been made which are reported in the present communication. Although one sees patients occasionally who require large quantities of insulin, almost invariably a responsible complication can be disclosed, and, even so, the total daily dose rarely exceeds 100 units. The case to be described is without parallel in a group of approximately 11,500 patients with true diabetes seen in this clinic since the introduction of insulin in 1922. The only other patient in our series with an enormous insulin requirement was a doctor with hemochromatosis, previously reported on,¹ who died in coma despite a final dosage of 1,680 units of insulin a day. His case differed materially from that of the woman under discussion, however, in that the course was rapidly progressive and the insulin resistance was satisfactorily explained by the complicating hemochromatosis.

REPORT OF CASE

Mrs Helen St C, of French-Canadian parentage, a former nurse, was admitted to the New England Deaconess Hospital on July 2, 1935. She had been transferred from a hospital in a neighboring city.

I *First Hospitalization* (July 2, 1935 to April 29, 1936) —Family History. The patient's father was living at the age of 75 and was well except that he had complained of arthritis since the preceding winter. Her mother was living and well at 65 years of age. There were five brothers, aged 20 to 37 years, and five sisters, aged 19 to 39 years, who were living and well. Five uncles and aunts were living and well. There was no history of arthritis or diabetes in the family other than as previously mentioned.

From the George F Baker Clinic, Dr Elliott P Joslin, medical director, New England Deaconess Hospital.

The expenses of the studies, other than those of a routine nature, which are reported in this paper were defrayed in part by a grant from the Chemical Foundation, Inc.

1 Root, H F. Insulin Resistance and Bronze Diabetes, *New England J Med* 201:201 (Aug 1) 1929.

Past History The patient was born on April 17, 1900, in Ontario, Canada. She was graduated from the nurses' training school of a large general hospital in Toronto, Canada, in 1920 and in 1923 took postgraduate work at a maternity hospital in New York. She continued nursing until about 1931. She lived in New York off and on between 1928 and 1932. Since 1932 she had lived in a city in Massachusetts.

The patient was married in May 1925, a year or two after coming to the United States from Canada. There was one miscarriage in 1926, and in 1931 a son was born who suffered periodic convulsions owing to an injury at birth. The patient's husband was about 45 years of age and had asthma, but there was no history of diabetes in his family.

Operations The following operations had been carried out: 1922, tonsillectomy, 1926, dilatation and curettage for incomplete miscarriage, 1928, appendectomy, oophorectomy and ventral suspension of the uterus, May 1935, hemorrhoidectomy.

Illnesses Except for measles in childhood, pneumonia at the age of 19 and attacks of tonsillitis prior to the operation in 1922, the patient had had no noteworthy illnesses.

Present Illness The first signs of arthritis were noted in 1926, when there was involvement of both shoulders. She noticed the pain at this time chiefly when lying down. She was not ill enough to go to bed and continued at her work of nursing at a hospital in New York. The disability lasted from about the spring to the fall of 1926. Then followed a period of quiescence, and it was not until about October 1932, while she was still in New York, that symptoms of arthritis reappeared. At this time the right elbow was the first joint affected, and after this the feet and ankle joints were involved. The arthritis was at first migratory, and the joints were swollen, red and tender. Rheumatic fever was suspected at the time, but the patient never had fever. During the summer of 1933 the arthritis was severe, and from this time on the patient was actively treated for this disease by doctors in New York and Massachusetts. For the several months prior to April 1935 her condition was poor, and although she was never confined entirely to bed, she was a semi-invalid.

The date of onset of diabetes is difficult to establish. It is true that for an indefinite period the patient had suffered polyuria and polydipsia, but she could remember no time at which there was an increase in thirst or in the quantities of urine voided. She stated that she was in the habit of drinking large amounts of water along with the medicine given to her for arthritis. She recalled that in November 1933, at a visit to her doctor, she weighed 105 pounds (47.6 Kg) dressed, and it was remarked at the time that she was losing weight. It must be remembered, however, that she was then suffering from chronic arthritis. Unfortunately her physician did not obtain a specimen of urine at that time. It seems fairly certain that in about 1932 the urine was examined and declared free from sugar.

The patient was admitted to a hospital in a city close to Boston on April 22, 1935. Several days before entry her local physician told her that she had "about 10 per cent sugar in the urine." During this hospitalization the patient was much improved and was discharged on June 7. She returned thirty hours later, on June 8, in impending diabetic coma. Because of the fact that her diabetes was difficult to control and because some endocrine disturbance other than the diabetes was suspected, she was transferred to the New England Deaconess Hospital.

Examination When the patient was admitted to the New England Deaconess Hospital on July 2, 1935, she was seen to be poorly nourished. Her height was 64 inches (162.6 cm), and her body weight (stripped) was 84¾ pounds (38.5

Kg) She looked pale. The heart was of normal size and had a regular rhythm, and no murmurs were heard. The lungs were clear, the abdomen was soft and nontender, the spleen was palpable and the kidneys were palpable but not enlarged. The circulation to the feet seemed good. The blood pressure was 100 systolic and 60 diastolic. A Hinton test of the blood gave negative results. The urine on entry contained 19 per cent sugar, a negligible amount of albumin and no bile or diacetic acid. The blood sugar content during fasting was 0.25 per cent, and the nonprotein nitrogen content was 28 mg per hundred cubic centimeters.

Roentgenograms of the chest on July 12 showed the cardiac shadow and the pulmonary markings to be within normal limits. Roentgenograms taken on July 25 showed the bones of the skull to be thick and dense, the pineal gland calcified and the sella turcica normal in size and regular in contour. Pyelograms taken after the intravenous injection of an opaque solution on July 27 revealed hydronephrosis on both sides, with considerable extrarenal dilatation and a sharp kink at the ureteropelvic junction on the right. (The patient had not had nor has she since had any symptoms directly referable to these abnormalities.) The findings as regards the joints will be discussed later.

Course in the Hospital. 1. Diabetes. The patient remained in the hospital until April 29, 1936, about ten months. The course was most extraordinary and is set forth graphically in figure 1. It was soon found that the diabetes was not of the usual type, because at the end of the first week even with a low diet (carbohydrate, 120 Gm, protein, 56 Gm, and fat, 84 Gm), making a total of 1,400 calories per day, she excreted in the urine during a typical twenty-four hour period considerable diacetic acid and acetone and 39 Gm of sugar, although she was receiving a little over 100 units of insulin during the day. Accordingly the dose of insulin was gradually increased in an attempt to control the excretion of sugar. Because of her extreme hunger and our desire to relieve her emaciated condition, the diet was also increased at regular intervals. Accordingly, about a month after entry, with a diet containing 148 Gm of carbohydrate, 86 Gm of protein and 107 Gm of fat, making a total of 1,899 calories per day, she was receiving 196 units of insulin. She still showed a yellow, red or orange reaction to the Benedict test for sugar throughout the day. On October 23 she was given 530 units of insulin in six doses. By November 2, four months after entry, she was receiving 475 units of insulin a day, and this was with a liberal diet (carbohydrate, 200 Gm, protein, 112 Gm, and fat, 141 Gm, making a total of 2,570 calories per day). The urine was by no means free from sugar, however. In order to test the influence of the amount of carbohydrate in the diet on the insulin dosage, this was gradually reduced to 120 Gm a day. It was found, however, that such a reduction did not materially decrease the amount of insulin required, and even with 120 Gm of carbohydrate, 107 Gm of protein and 143 Gm of fat (2,197 calories a day), she required 470 units of insulin (fig 1). It was demonstrated by lengthy trials that the type of insulin was not a factor, the patient was given pure beef insulin, beef and pork insulin, pure pork insulin and crystalline insulin². Different brands were tried, but no difference was noted.

It was repeatedly demonstrated during this and subsequent hospitalization that failure to supply sufficient insulin resulted in a prompt flareup of hyperglycemia and glycosuria. Contrariwise, when too much insulin was given, typical hypoglycemic symptoms resulted. In other words, this patient reacted to treatment

2 The crystalline insulin was supplied by Prof. C. H. Best, of the University of Toronto, and the special pork insulin by Eli Lilly & Co.

as does the patient with straightforward diabetes except that the amount of insulin required for control was roughly ten times that required by the average patient with moderately severe diabetes

On January 4, because of marked induration of the skin and atrophy of the subcutaneous fat over the thighs, due to repeated injections of large amounts of insulin, the site of administration was changed to the abdominal wall. The consequences of this were unexpected and most extraordinary. At about 10 p m the patient noted symptoms of hypoglycemia, the blood sugar value at that time

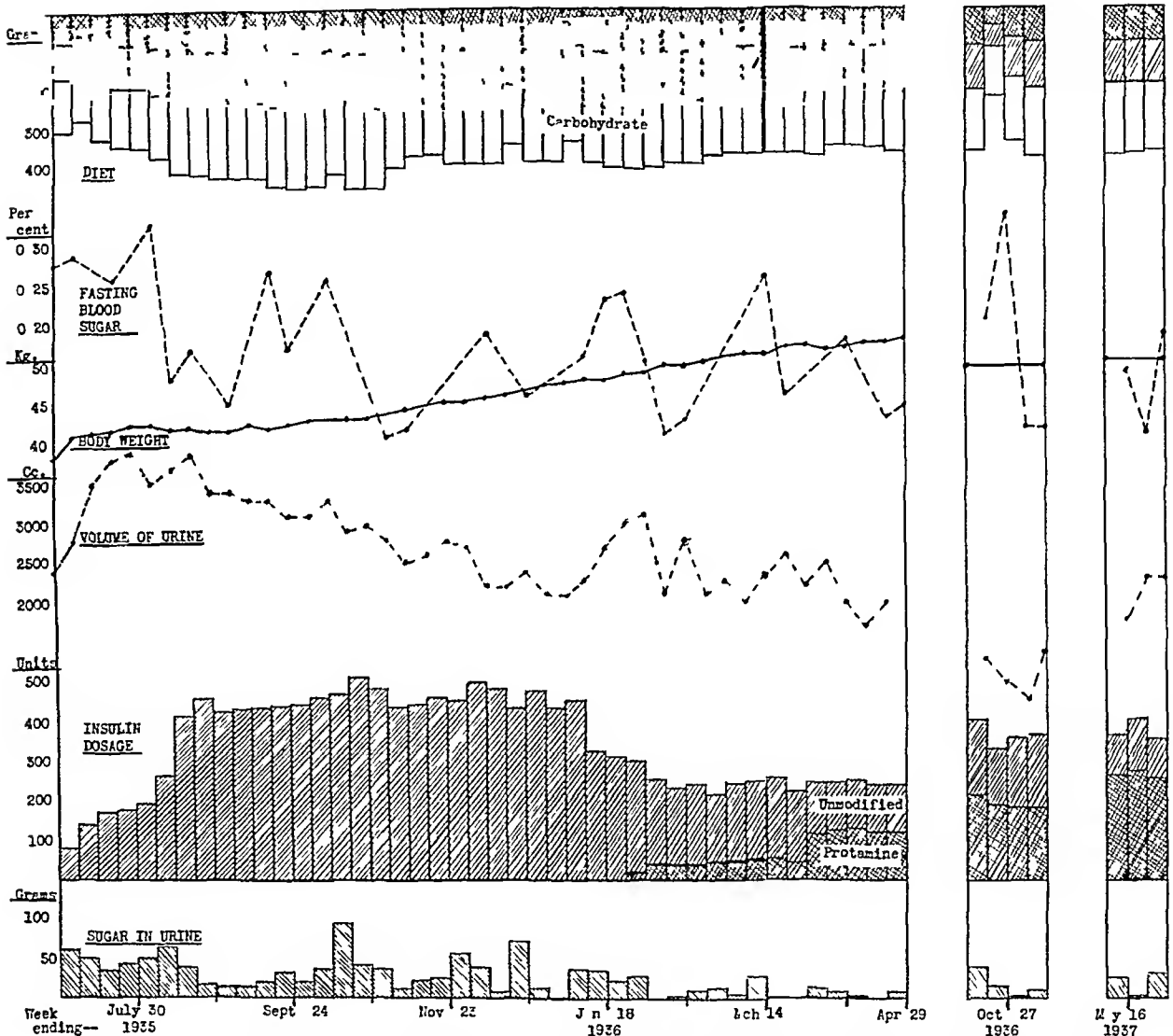


Fig 1—A chart summarizing the data obtained during the course of the patient's three periods of hospitalization. Each block on the chart gives average values for one week.

was found to be 0.04 per cent. Orange juice gave relief, and the patient slept the rest of the night, but at 6 a m she awakened with severe headache in the occipital region of the type experienced in prolonged though not severe hypoglycemia. The blood sugar value at 7:30 a m was 0.07 per cent. Because of this the dose of insulin was lowered and after a few days of adjustment was stabilized at a level of 300 to 340 units a day, approximately 100 units lower than before the site of injection was changed.

This effect was so striking that on February 1 the site was again changed, this time to an entirely fresh area on the flanks. Before the change the daily dose averaged 300 units. With continuance of injection of this amount in the fresh area, again prolonged hypoglycemia was produced, and after a few days of adjustment a new total of 240 to 260 units was found adequate.

This experience demonstrated anew and conclusively the value of insisting that the diabetic patient change the site of injection from one time to the next so that no one spot receives insulin oftener than every three or four weeks. Only in this way can the full value of the insulin be uniformly secured. Effects such as those secured in this case ordinarily pass unnoticed because of the differences in doses involved, changes being evident in the average case on a scale only one-tenth as great.

On January 23 the first dose of protamine insulin (Danish)³ was administered to this patient. It was given simply as a supplementary dose of 20 units at 10 a. m. As time went on, bolder use was made of it by gradual stages, finally, on April 7, simply 120 units of regular (unmodified) insulin plus 120 units of protamine insulin (Danish) was given in two injections at one time in the morning before breakfast, and then no more insulin was given during the rest of the day. The results far exceeded our expectations. Instead of six injections of regular insulin daily as before, the diabetic condition was then under good control with insulin administered only once a day. On the morning before her discharge, the blood sugar content during fasting was normal, 0.10 per cent. On discharge (April 29) the patient was instructed to take 120 units of unmodified and 120 units of protamine insulin (Danish)⁴ each morning.

2 Glandular enlargement. On Sept. 12, 1935, it was noted for the first time that the patient had general glandular enlargement involving the cervical, axillary, epitrochlear and inguinal regions but most marked in the last-named location, so much so that she had a great deal of pain in the groins, particularly on the right. This glandular enlargement persisted to a marked degree until April 1936. Histologic examination of a node taken from the left axilla showed only chronic inflammation. The liver and spleen were always palpable. Roentgenograms revealed no mediastinal nodes or calcified abdominal nodes. Because of the splenomegaly, arthritis and leukopenia, the diagnosis of Felty's⁵ syndrome was at one time considered.

3 Arthritis. The chief articular involvement at first was that of the knees and elbows, which during the first six months of hospitalization were markedly swollen, distended with fluid, somewhat tender to touch and painful on motion. To some extent the ankles, hips, shoulders and joints of the fingers and toes were affected. Later the right ankle was the chief joint involved. A surprising characteristic was the lack of limitation of motion, considering the amount of involvement. Roentgenograms of the various joints showed in most cases that the surfaces were well preserved, with little or no erosion of the bone or cartilage (figs. 2 to 4). Acute exacerbations of the arthritis (with little or no fever, however) were experienced at occasional intervals during the first six months,

3 Obtained through Dr. H. C. Hagedorn, of the Steno Memorial Hospital, Copenhagen, Denmark.

4 To be comparable to the American preparations of protamine insulin that were used later, all doses of the Danish variety should be multiplied by eleven-fifteenths.

5 Felty, A. R. Chronic Arthritis in the Adult, Associated with Splenomegaly and Leukopenia, *Bull. Johns Hopkins Hosp.* **35** 16 (Jan.) 1924.

but the general tendency was toward improvement, and at the time of discharge (April 29) there was little or no fluid in any of the joints, and motion everywhere was remarkably free, although of course there was well marked generalized deformity, with crepitus easily audible, particularly in the knee joints

Treatment for the arthritis consisted of prolonged rest at first, followed by gradually increasing exercise, passive motion and massage and the use of contrast baths, radiant heat and analgesics

4 Hematologic findings When the patient was admitted to the hospital the erythrocyte count was 4,510,000, and the hemoglobin value was 70 per cent (Sahli) During the next three weeks the values fell to a level of 3,900,000 and 63 per cent, respectively, presumably because of the retention of fluid in the body and relief of dehydration of the tissues During the ensuing weeks and months, coincident with the giving of ferrous sulfate orally in doses of 12 grains (0.78 Gm) daily,

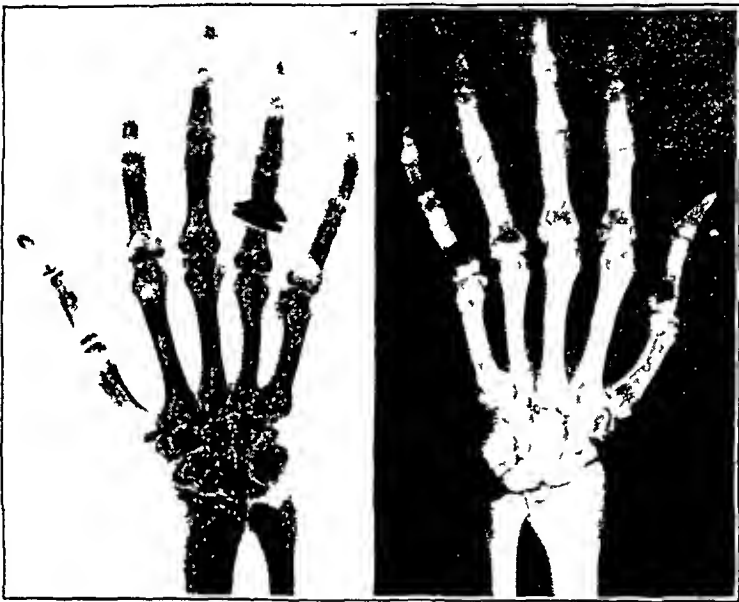


Fig 2—Roentgenograms of the hands showing arthritic changes, with narrowing of the articular spaces and swelling of the soft parts Note also rarefaction of the bone at the ends of the metacarpal bones and the phalanges

the anemia gradually disappeared, and during the last four months of hospitalization the red blood counts varied between 4,410,000 and 4,980,000 and the hemoglobin values between 80 to 96 per cent

Prior to her entry (July 2, 1935) the white blood cell count obtained elsewhere had varied from 3,800 to 4,700 The first count at the New England Deaconess Hospital gave a value of 7,050, and no figure below 5,800 was obtained until August 1 From this time until September 2 the counts varied from 3,900 to 5,450 During the subsequent eight months the values were within normal limits, ranging from 5,600 to 11,600 but usually from about 7,000 to about 8,500

The most striking hematologic finding was that of eosinophilia Studies elsewhere just prior to entrance showed only 2 per cent eosinophils, and the blood smear made on entry showed this same value On August 26, however, 15 per cent eosinophils was noted, and from then on abnormally high values were the rule The highest percentages were 31 on September 27, 36 on November 13, 33 on January 14, and 33 on April 8 In the absence of any other cause, it seems

reasonable to conclude that the eosinophilia was part of an allergic response provoked by the extremely large doses of insulin. Such a finding has been reported by Lawrence⁶ and Lawrence and Buckley⁷.

5 Disease of the endocrine glands other than the pancreas. Because in the earlier part of the patient's stay in the hospital the basal metabolic rate was regularly found to be +25 or +26 per cent, hyperthyroidism was considered as a diagnosis. However, with only rest in bed and no specific therapy, the basal metabolic rate gradually fell so that the last determination of a given series was +7 per cent, and on Oct 17, 1936, it was +1 per cent. The iodine content of blood taken with the patient in the fasting state (2 micrograms per hundred cubic centimeters of blood), when considered in connection with a normal blood iodine curve after the giving of 50 mg of iodine by mouth, did not suggest



Fig 3—Roentgenograms of the knees, showing arthritic changes, with narrowing of the articular spaces, swelling of the soft parts and generalized rarefaction of bone.

hyperthyroidism⁸. Her creatine tolerance was found to be low, after receiving 1 Gm of creatine by mouth, she excreted 60 per cent of it in the urine within twenty-four hours. Although this is compatible with hyperthyroidism, it is not pathognomonic and might well be a finding in any chronic wasting disease.

It is of interest that in March 1936 the patient began menstruating for the first time in ten months.

Roentgenograms of the skull showed no enlargement of the sella turcica, and examination of the eyegrounds revealed no abnormality. There was nothing other than the insulin resistance which suggested pituitary disease. In the hope

6 Lawrence, R. D. Studies of an Insulin Resistant Diabetic, *Quart J Med* **21** 359 (April) 1928.

7 Lawrence, R. D., and Buckley, O. B. Eosinophilia in Insulin Therapy, *Brit M J* **1** 597 (March 30) 1929.

8 These studies were carried out under the direction of Mr. H. J. Perkin, of the Lahey Clinic.

of demonstrating the presence in the blood of some substance possessing hyperglycemic or diabetogenic activity, 5 to 55 cc of (fasting) blood serum from the patient was injected intravenously into a 3,720 Gm white male rabbit on three successive days, and on the third day 74 cc of 50 per cent dextrose was administered intravenously (with the rabbit in the postabsorptive state) two hours after the giving of the patient's serum. Serial determinations of the blood sugar content were then made at frequent intervals for over three hours. The results were conclusively negative, in that the dextrose tolerance curve obtained differed

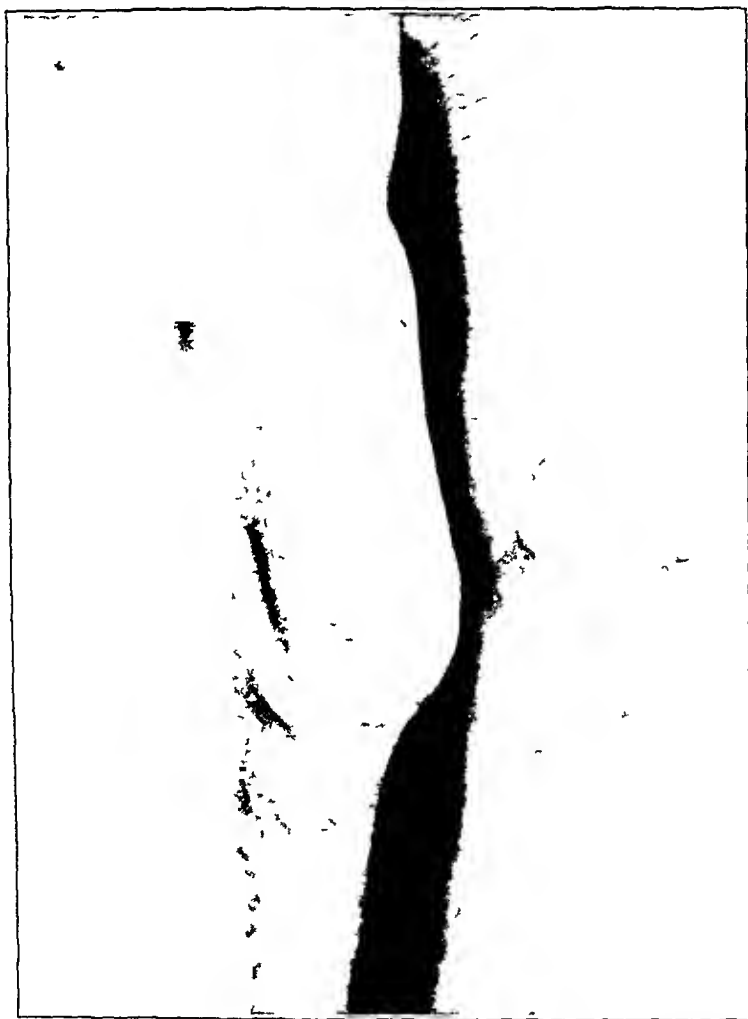


Fig 4—Anterior view of the legs, showing arthritic deformity at the knees and areas of atrophy of subcutaneous fat over the thighs

in no significant detail from two control curves previously obtained for the same rabbit (using a comparable technic but without the injection of the patient's serum). It would be of interest to know whether or not injection of this patient's serum into a rabbit would modify the curve obtained after the injection of a suitable dose of insulin. With this procedure an antagonistic effect has been observed by de Wesselow and Griffiths,⁹ particularly with blood serum of elderly, obese diabetic patients, but in our own limited experience we have been unable to corroborate these findings.

⁹ de Wesselow, O. L. V., and Griffiths, W. J. On the Possible Role of the Anterior Pituitary in Human Diabetes, *Lancet* 1 991 (May 2) 1936

6 Other features No infection other than arthritis was demonstrated Roentgenograms of the chest showed no evidence of tuberculosis A biopsy of the skin showed no hemosiderin, nor did at least three examinations of the urinary sediment by the method of Rous¹⁰ give any support to the diagnosis of hemochromatosis Tests for Bence Jones protein in the urine repeatedly gave negative results The chloride and uric acid contents of the blood serum were normal, and the total cholesterol content of the plasma was low normal, varying from 125 to 136 mg per hundred cubic centimeters One determination of the gastric contents showed no free hydrochloric acid, and this was confirmed by fractional aspiration after a test meal of 100 cc of 7 per cent alcohol, samples being taken during fasting and at intervals of fifteen minutes for an hour after the test meal

Excretion of Nitrogen in the Urine

Date	Urine, 24 Hour Amount			Diet	
	Volume, Cc	Total Nitrogen		Protein (Calculated), Gm	Nitrogen (Average), Gm
		Gm per Day	Average, Gm		
1935					
Aug 13 14	3,600	12.5		102	
14 15	4,300	13.9		102	
15 16	3,600	15.4	13.9	108	16.3
Oct 22 23	2,100	11.4		112	
23 24	2,600	11.8		112	
24 25	3,185	14.9	12.7	112	17.9
Nov 20 21*	2,300	19.1		107	
21 22	2,700	16.7		107	
22 23	2,300	13.3	16.4	107	17.1
1936					
April 17 18	1,630	11.9		96	
18 19	1,750	9.3		96	
19 20	1,850	10.1	10.4	96	15.4

* In retrospect it is difficult to explain the variation in results obtained during the three days in November Unfortunately, no creatinine values are available as a check on the accuracy of the collections of urine

The phenolsulfonphthalein test of renal function gave normal results, with an excretion of 60 per cent of the dye in two hours and ten minutes The bromsulphalein test of hepatic function showed normal clearance of the dye from the blood stream Of twelve tests for urobilinogen (scattered over a period of months) in twenty-four hour specimens of urine, two were reported as showing a positive result in 1:10 dilution, two in 1:20, four in 1:30, three in 1:50 and one (faintly) in 1:100 Since the results of the test (method of Wallace and Diamond¹¹) are regarded as abnormal if a positive reaction is obtained in dilutions over 1:20, there was some suggestion of hepatic impairment in this case

The total nitrogen content of the urine on representative days is shown in the accompanying table The figures indicate a greater or less degree of nitrogen

10 Rous, P Urinary Siderosis Hemosiderin Granules in the Urine as an Aid in the Diagnosis of Pernicious Anemia, Hemochromatosis, and Other Diseases Causing Siderosis of the Kidney, J Exper Med 28:645 (Nov) 1918

11 Wallace, G B, and Diamond, J S The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch Int Med 35:698 (June) 1925

retention This might be expected, since during this period the body weight and strength had been steadily increasing Values for ammonia nitrogen in the urine were found in April 1936 to vary from 0.37 to 0.58 Gm per twenty-four hours, or from 3.9 to 4.9 per cent of the corresponding values for total nitrogen

At discharge the patient weighed $117\frac{1}{4}$ pounds (53.3 Kg), or $32\frac{1}{2}$ pounds (14.8 Kg) more than on entry ten months previously! This attests as much as anything else to her great improvement during this period

II *Second Hospitalization* (Oct 13 to Nov 8, 1936)—The patient was readmitted to the hospital on Oct 13, 1936, for further study During the five and one-half months at home she had been in fair condition although handicapped greatly by arthritis With the aid of crutches she had been able to be up and around for part of each day She complained of nervousness and irritability and of painful bleeding hemorrhoids Although at the time of entry the dose of insulin was 150 to 200 units of regular (unmodified) insulin and 240 units of protamine insulin (Danish) once daily in the morning before breakfast, she had taken during the summer as much as 400 units of unmodified insulin and 275 units of protamine insulin (total 675 units) a day She had kept her diet at a level of 150 Gm of carbohydrate, 100 Gm of protein and 110 Gm of fat a day Menstrual periods had been occurring every three weeks, lasting usually for six or seven days, with excessive flowing for three days of that time

On physical examination the heart and lungs were found to be essentially normal, and the blood pressure was 95 systolic and 60 diastolic The liver could be felt to descend 3 cm below the costal margin in the mamillary line, and the spleen could be felt to descend 1 to 2 cm A few small cervical, practically no axillary, one small right epitrochlear and several inguinal nodes on each side could be felt Even the last-named glands, however, were appreciably smaller than on the first entry One right inguinal node was slightly tender There were subcutaneous lumps over the thighs and abdomen at the sites of injections of insulin Pelvic examination indicated an essentially normal condition The urine contained no albumin The erythrocytes numbered 4,470,000 and the white blood cells 7,450 per cubic millimeter The hemoglobin value was 85 per cent, a blood smear showed neutrophils, 44 per cent, lymphocytes, 33 per cent, and eosinophils, 23 per cent The basal metabolic rate was $+1$ per cent

On October 20 incision and curettage of an anal fissure and dilatation of the anal sphincter were carried out by Dr T C Pratt, with the patient under spinal anesthesia The postoperative course was uneventful Incidentally, spinal fluid removed just before the operation gave a negative reaction to the Wassermann test, microscopic examination of the undiluted fluid in a counting chamber showed only 2 cells in the entire field

During her stay in the hospital the patient's diet contained 167 Gm of carbohydrate, 84 Gm of protein and 115 Gm of fat The diabetic condition was kept under control with 180 units of unmodified and 180 units of protamine insulin (Squibb) daily, simultaneous doses being given before breakfast (fig 1)

At this time it was found that the capsular tissue of both knee joints was loose, apparently because of the absorption of the long-standing effusion which had in the past caused much stretching Hence inadequate support was available, and there was a marked tendency for the patient's legs to give way when she attempted to walk This was partly corrected by making a brace for the left knee

III *Third Hospitalization* (May 9 to 30, 1937)—The patient again entered the hospital on May 9, 1937, for a stay of three weeks During the six months since her second entry she had improved in strength, and she looked better in

general There had been no acute exacerbation of arthritis, although her activity was still markedly limited because of articular pain She had taken from 280 to 430 units of insulin daily The findings on physical examination did not differ greatly from those at the last entry, although there was if anything less activity as regards the arthritic process, the general glandular enlargement was less striking and the spleen could not be felt There was no anemia, the white blood cell count varied from 6,300 to 9,400 and the percentage of eosinophils varied from 5 to 12 The body weight was 110 to 111 pounds (50 Kg) On discharge the patient was advised to follow a diet calling for 167 Gm carbohydrate, 84 Gm of protein and 130 Gm of fat daily and to take 100 units of unmodified insulin and 300 units of protamine zinc insulin daily at one time in the morning before breakfast

During this stay in the hospital, through the cooperation of Dr J H Marks, roentgenologist, six irradiations of the skull (hypophysial region) were given, one each day for six consecutive days (May 24 to 29, 1937, a total of 1,200 roentgens [400 kilovolts] over a field [6 by 6 cm] in each temporal region) No alteration of the insulin requirement was noted then or subsequently¹¹ This experience is contrary to that reported by Merle,¹² Pieri and Sarradon¹³ and Cannavo¹⁴

COMMENT

In certain of the cases of marked resistance or refractoriness to insulin reported in the literature, some factor has been apparent to which it seemed reasonable to assign the responsibility for the condition Thus the patient reported on by Altshuler and Gould¹⁵ was found post mortem to have a large suprasellar cystic hematoma which pressed on the optic chiasm, hypophysis and neighboring structures In Wayburn's¹⁶ case there was extensive pulmonary tuberculosis, in Warvel's¹⁷ a pineal tumor and in Engel's¹⁸ and Root's¹ hemochromatosis In other instances no cause has been apparent In the case reported by

11a Note added on June 30, 1938 Since this paper was submitted for publication a further attempt has been made to demonstrate an influence from irradiation of the skull From April 13 to 27, 1938, twelve irradiations of 300 roentgens each were given over a field 4 cm in diameter in each temporal region at a distance of 50 cm, a total of 3,600 roentgens (200 kilovolts) No significant effect on the diabetic condition or on the insulin requirement has been noted

12 Merle, E Diabete grave insulino-resistant Reduction brusque et massive de l'insulino-resistance par irradiation de la region hypophysaire, Bull et mém Soc med d hôp de Paris **51** 35 (Jan 21) 1935

13 Pieri, J, and Sarradon, P Diabete grave insulino-resistant Reduction notable de l'insulino-resistance par la radiotherapie hypophysaire, Bull et mem Soc med d hôp de Paris **51** 1579 (Dec 2) 1935

14 Cannavo, L Insulinoresistenza e irradiazioni rontgen della regione ipofisaria, Policlinico (sez prat) **43** 1099 (June 15) 1936, abstracted, J A M A **107** 545 (Aug 15) 1936

15 Altshuler, S S, and Gould, S E Diabetes Refractory to Insulin, with Report of a Case, Ann Int Med **9** 1595 (May) 1936

16 Wayburn, E Complete Insulin Resistance in Diabetes, Am J M Sc **190** 157 (Aug) 1935

17 Warvel, J H Personal communication to the author

18 Engel, R Insulinrefraktärer Diabetes bei schwerem Leberschaden, Klin Wchnschr **13** 1682 (Nov 24) 1934

Clay and Lawrence¹⁹ there was found at postmortem examination no adequate explanation for the unusual requirement of insulin, which reached 960 units during the last twenty-four hours of life. It is true that this 63 year old man had pernicious anemia (controlled) and heart disease in addition to diabetes. Mason and Sly²⁰ concluded that the resistance of their patient was due to a "marked lessening of the liver's ability to convert dextrose to glycogen or an intermediate product in this conversion." In their patient, a 25 month old boy, glycosuria could be almost stopped by the substitution of levulose or galactose for dextrose in the diet. Unfortunately no postmortem examination was allowed in the extraordinary case reported by Thannhauser and Fuld,²¹ in which, despite large amounts of insulin (200 to 240 units a day) for several days and 1,230 units (170 units subcutaneously and 1,060 units intravenously) on the final day, death took place in coma.

Reviews of the subject from different approaches are to be found in the papers by Falta and Boller,²² Pollack²³ and Aubertin.²⁴

The cause of the extraordinary insensitiveness to insulin exhibited by the patient reported on in the present paper is an interesting problem. The following possibilities suggest themselves.

1 Hemochromatosis. Against this diagnosis were the absence of the characteristic color of the skin and the negative results of tests for iron pigment in the skin at biopsy and in the cells of the urinary sediment. Moreover, as time has gone on, the patient's general condition has improved (it has not become progressively worse, as in our other case, reported on by Root¹), and the enlargement of the liver and spleen, never great, has become less.

2 Infection. The only significant infection which has been demonstrated in this patient is that of rheumatoid arthritis. However, only occasionally has there been enough activity to cause fever, and, even then, various consultants, specialists in orthopedic and arthritic disorders, have agreed that this infectious process was in no way adequate to account for the startlingly high requirement of insulin. Furthermore,

19 Clay, P. D., and Lawrence, R. D. Insulin Resistance, *Brit. M. J.* **1** 697 (April 6) 1935.

20 Mason, H. H., and Sly, G. E. Diabetes Mellitus. Report of a Case Resistant to Insulin But Responsive to a Change in the Type of Carbohydrate. *Fed. J. A. M. A.* **108** 2016 (June 12) 1937.

21 Thannhauser, S. J., and Fuld, H. Insulinmangelkoma und Insulinrefraktäres Koma im Verlaufe eines Diabetes mellitus, *Klin. Wchnschr.* **12** 252 (Feb 18) 1933.

22 Falta, W., and Boller, R. Insularer und Insulinresistenter Diabetes, *Klin. Wchnschr.* **10** 438 (March 7) 1931.

23 Pollack, H. Conditions Associated with Unusual Requirements for Insulin, *Proc. Staff Meet., Mayo Clin.* **8** 453 (July 26) 1933.

24 Aubertin, E. L'insulinorésistance, *Bruxelles-med.* **16** 453 (Jan 26) 1936.

during the past year, while the arthritic process has been relatively quiescent, the large doses of insulin have had to be continued

Physical examination and roentgenograms have given no evidence of pulmonary tuberculosis Wayburn¹⁶ said he regarded this condition as responsible for the extraordinarily large requirement of insulin in the case reported by him

3 Disorders of the endocrine glands other than the pancreas As far as possible pituitary disease has been excluded as a cause, although the means available today are admittedly inadequate to show functional disorders Roentgenograms have shown the sella turcica to be normal, examination has always shown the eyegrounds to be normal and irradiation of the skull daily for six days produced no effect on the requirement for insulin The moderate elevation of the basal metabolic rate obtained in earlier observations brought up the question of overactivity of the thyroid gland, but clinical findings and other laboratory tests have not been consistent with this diagnosis, later determinations of the basal metabolic rate have given normal results The normal blood pressure and the absence of signs of Cushing's syndrome are against dysfunction of the adrenal glands Roentgenograms of the skull have shown calcification in the region of the pineal gland, but this is so frequently seen in roentgenograms that its significance is questionable The possibility of a disturbance in this organ was thought of because of Warvel's¹⁷ remarkable case of a girl who received extraordinarily large amounts of insulin over a period of ten months and at postmortem examination (after death in diabetic coma) was found to have a pineal tumor Related ovarian dysfunction was evident in our own patient in view of the fact that she did not menstruate from May 1935 to March 1936, but the amenorrhea was undoubtedly an effect rather than a cause

4 Extensive pancreatic disease—structural or functional It is conceivable that marked destruction of the islet-containing tissue of the pancreas might cause diabetes with a large requirement of insulin for its control In our patient no sign of a tumor or of inflammatory disease of the pancreas has appeared Furthermore, the amount of insulin necessary to control hyperglycemia and glycosuria is larger than that which Root¹ said he regarded as the requirement of a completely depancreatized man, namely, 200 to 300 units daily Although the evidence is wholly indirect, it is entirely possible that the pancreas of our patient secretes an amount of insulin approaching the normal and that the chief abnormality is due to extrainsular influences

5 Miscellaneous conditions Diabetic acidosis or coma, which temporarily almost invariably calls for an increased amount of insulin, has obviously not been a factor in our case Also there has been no suggestion of cardiac decompensation²³

6 As regards many obscure metabolic problems, one invariably turns to the liver in searching for an explanation of phenomena observed. The liver is a great transforming agent not only of carbohydrate but also of protein and fat, storing, yielding up or modifying these substances as bodily needs arise. One of the characteristics of diabetes mellitus is the inability of the body to maintain normal stores of glycogen in the liver. Instead, dextrose floods the blood and body tissues generally. Furthermore, possibly as a result of hypophyseal action and possibly also by virtue of the mediation of the adrenal cortex,²⁵ dextrose is formed in excessive amounts from noncarbohydrate sources. Insulin in proper doses corrects these abnormalities, as well as promotes normal utilization of dextrose in the tissues. It is possible that in our patient glycogenolysis and the new formation of sugar from protein and fat proceed with such ease and the opposite chemical changes proceed with such difficulty, possibly because of hormonal influences, such as those from the pituitary body or the adrenal cortex, that enormous amounts of insulin are necessary to main the proper balance. We do not know to what extent, if any, in our patient utilization of dextrose in the tissues proceeds less normally than in the usual diabetic patient.

Other possibilities are that there exists in the blood and tissues some agent which in a more direct way than has been suggested may oppose or neutralize the action of insulin²⁶ or that some enzyme needed for the activation of insulin, such as an "insulin-kinase,"²⁷ is deficient because of a defect of the pancreas or of the liver. These possibilities, although interesting, find no support in concrete data. Furthermore, somewhat rough tests (assay in mice) have not supported the possibility that the huge amounts of insulin given our patient are in large part excreted in the urine.

The patient is being kept under close observation in the hope that the solution of her problem may throw light on the problem of diabetes in general.

SUMMARY

A report is made of a patient with marked insensitiveness to insulin who has been observed closely since July 1935. This woman (who was 35 years of age when first seen) has chronic rheumatoid arthritis. The insulin requirement has varied from 240 to 675 units daily.

25 Long, C. N. H. The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, pp. 194-228.

26 Fitz, R. Does Diabetic Blood Contain an Insulin-Inactivating Substance? in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 446.

27 Himsworth, H. P. The Activation of Insulin, *Lancet* **2**: 935 (Oct. 29) 1932.

Complications other than the arthritis have included marked general glandular enlargement, slight to moderate hepatomegaly and splenomegaly and eosinophilia of striking degree. The last-named complication has been attributed to the large doses of insulin.

The occurrence of lipodystrophy at the site of the injections of insulin has been a problem.

In a striking way it has been demonstrated that injection of insulin into areas of tumefaction and scarring (produced by multiple previous injections) is less effective in lowering the blood sugar than injection into a normal area.

Control of the diabetic condition has been followed by a gratifying gain in weight and strength.

Attempts to demonstrate a pituitary, adrenal, thyroid or gonadal influence as being responsible for the resistance to insulin have been unsuccessful as far as direct evidence is concerned. Other possible causes for the condition, including hepatic dysfunction and abnormal excretion of injected insulin, are discussed.

NOTE (June 30, 1938) —After the completion of the foregoing report, the patient was studied again during a fourth visit to the hospital, on April 10 to May 4, 1938. There had been no essential change in her condition. Prior to entry she had been taking 100 units of unmodified and 160 units of protamine zinc insulin daily. In the hospital it was possible to reduce for a few days the amount of insulin to a total of 150 units of the unmodified type (no protamine insulin). However, the requirement then rose so that on the day of discharge 150 units of unmodified plus 220 units of protamine zinc insulin was given. The patient had noted at home definite unexplained variations in the insulin requirement from time to time. She had been menstruating regularly about every twenty-eight days, she had noted no relation between the menstrual periods and the insulin requirement.

The body weight without clothing was 116 pounds (52.7 Kg). Physical examination showed both the liver and the spleen to be palpable. Roentgenograms of the chest and skull showed no significant abnormalities. Those of the joints, especially the joints of the hands and wrists, showed marked loss of cartilage and erosion of the articular spaces, indicating much progression of the arthritic process since November 1935. The basal metabolic rate was -1 per cent, the visual fields were normal, the blood sedimentation rate was normal and the plasma cholesterol value was 116 mg per hundred cubic centimeters. The erythrocyte count was 4,560,000, the hemoglobin value was 70 per cent (Sahli) and the eosinophils in the blood smear numbered 2 per cent. Marked insensitiveness to insulin was evident when the test devised by Himsworth²⁸ was carried out.

Drs. Mark H. Rogers, Theodore C. Pratt, Walter Bauer and others cooperated in the treatment of this patient during her long stay in the hospital.

28 Himsworth, H. P. Diabetes Mellitus. Its Differentiation into Insulin-Sensitive and Insulin-Insensitive Types, *Lancet* **1** 127 (Jan. 18) 1936.

PROTAMINE ZINC INSULIN

CLINICAL OBSERVATIONS AND COMPARATIVE ANALYSIS OF BLOOD
SUGAR CURVES OBTAINED WITH USE OF PROTAMINE
ZINC INSULIN AND WITH REGULAR INSULIN

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A considerable number of favorable reports on the clinical use of protamine zinc insulin in the treatment of diabetes mellitus have appeared in the literature. The articles of Joslin and his co-workers,¹ Rabinowitch and his co-workers,² Wilder³ and others may be cited as examples. In view of these reports there can be no question regarding the more prolonged action of protamine insulin as compared with that of insulin hydrochloride. It is also obvious that with constant proper laboratory supervision, it is possible to treat patients with diabetes mellitus satisfactorily with the newer forms of insulin and usually with a decrease both in the number of doses and in the quantity of insulin administered. Stress thus far has been on the favorable results and the advantages to be gained from a more uniform regulation of the level of blood sugar. Relatively little has been said of the difficulties encountered in the use of protamine zinc insulin. Certain difficulties nevertheless do occur even after considerable experience has been secured with the use of protamine insulin, sometimes when the patients

The insulin used in this study was supplied by Eli Lilly & Co., Indianapolis

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1 Joslin, E. P., Root, H. F., Marble, A., and White, P. Protamine Insulin, *New England J. Med.* **214** 1079-1085 (May 28) 1936. Joslin, E. P. Diabetes Today and Tomorrow, *Ann. Int. Med.* **10** 179-193 (Aug.) 1936.

2 (a) Rabinowitch, I. M., Fowler, A. F., and Corcoran, A. C. Observations on the Action of Protamine and Insulin in the Treatment of Diabetes Mellitus, *Canad. M. A. J.* **35** 124-129 (Aug.) 1936. (b) Rabinowitch, I. M., Foster, J. S., Fowler, A. F., and Corcoran, A. C. Clinical Observations with Protamine Zinc Insulin and Other Mixtures of Zinc and Insulin in Diabetes Mellitus, *ibid.* **35** 239-252 (Sept.) 1936.

3 Wilder, R. M. The New Insulin, *Minnesota Med.* **20** 6-15 (Jan.) 1937. Wilder, R. M., and Wilbur, D. L. Disease of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **59** 329-364 (Feb.) 1937.

are under care in the hospital but especially when they are not under constant supervision. The use of protamine insulin rather quickly brings to light certain irregularities in its effect on the blood sugar which are likely to be particularly important if the drug is to be introduced in general practice for use by physicians who do not have adequate laboratory control of their patients.

Too much reliance cannot be placed on the urinary sugar value as a measure of the blood sugar value. We have noted frequently that the blood sugar level may be very high and that the urine may contain little or no sugar, and, conversely, sugar has been found to be present in the urine, although the blood sugar level at that time has been within normal limits. This observation is illustrated in many of the cases in the present study and leads one to believe that the renal threshold for sugar may vary in the same individual. The importance of obtaining frequent blood sugar determinations is therefore evident.

In the service for diabetic patients at the Firmin Desloge Hospital my colleagues and I have been quite successful in the use of protamine insulin in many cases. In other cases distinct difficulties have been encountered. We have felt that it would be of value to present frankly the difficulties we have experienced in using protamine insulin. Since one of the main advantages of the new type of insulin has been said to be the fact that fewer injections are required, we have endeavored in as many cases as possible to use one injection per day. Also, rather than complicate the treatment for the patients, we have avoided combining two types of insulin, and in some of the cases in which successful regulation of the carbohydrate metabolism has not been obtained with one dose of protamine insulin, we have tried to obtain it by dividing the dose in two. While it is obvious from the literature that a combination of the two types of insulin often gives good clinical results, it should certainly not be claimed in these instances that the management of the diabetic condition has been simplified by the use of the new preparation. In many cases it actually appears to have rendered treatment more complicated and difficult.

The present report will be confined to a study of 12 patients. Their ages varied from 24 to 70 years. The series included 2 patients who had been in diabetic coma on previous occasions. In all these cases satisfactory results were first obtained with regular insulin hydrochloride, and blood sugar readings were made at 7 and 11 a m., and at 3 and 7 p m. The patients were then given protamine zinc insulin. In most cases 75 per cent of the total number of units of regular insulin was given in the form of protamine insulin at 7 a m. as the initial dose. A period of five to six days was allowed to elapse in order to permit the cumulative effect of protamine zinc insulin to become defi-

nitely established. Then blood sugar readings were again made four times daily at the hours previously designated. If the values showed a satisfactory control of the carbohydrate metabolism during the day, an additional blood sugar reading was made at 3 a m to determine whether the metabolism of carbohydrate was satisfactory during the night. Specimens of urine were obtained four times daily, just before the venous puncture for the blood specimen was made. Patients were considered successfully treated with protamine zinc insulin if the blood sugar values with the protamine insulin regimen compared favorably with those obtained during the treatment with regular insulin. For patients unsuccessfully treated with one dose of protamin insulin, two doses were tried.

The effect of varying the time of administration of the protamine insulin was studied as well as the effect of altering the amount of carbohydrate given at each meal. All the patients were hospitalized for the first several weeks of this study. After their discharge from the hospital they returned to the outpatient clinic once a week, where their progress was observed and blood sugar determinations were obtained. Studies of the blood sugar were made with venous blood. The blood proteins were precipitated by the Folin-Wu method, and the blood sugar values were determined for the filtrate by the Shaffer-Somogyi improved copper-iodometric method.⁴

A brief résumé of each case will be presented, together with tables showing the blood sugar levels observed throughout the day, first with the use of regular insulin and then with protamine insulin. A comparison of the respective blood sugar curves can thus be made easily. In these tables the letter R represents regular or old insulin, and the letter P represents protamine insulin. The hours when the samples of blood were obtained and the insulin was administered are indicated in the headings for each table.

REPORT OF CASES

CASE 1—F Z was an electrician aged 47 years, weighing 76 Kg. Diabetes was discovered at the time of his first visit to the diagnostic clinic of the outpatient department, on Oct 16, 1936. When he was referred to the service for diabetic patients he was given a diet which consisted of 72 Gm of protein, 100 Gm of fat and 280 Gm of carbohydrate. Regulation of the carbohydrate metabolism was successful with this diet when three doses of regular insulin were given, distributed as 33 units in the morning, 17 units at noon and 31 units before the evening meal. The blood sugar curves for two consecutive days showed good control of the carbohydrate metabolism. The patient was then given 45 units of protamine zinc insulin at 7 a m, and blood sugar readings were made four times daily. After several days, as can be seen from the table, the curves compared favorably with those obtained when the patient was receiving regular insulin. In

4 Shaffer, P A, and Somogyi, M. Copper-Iodometric Reagents for Sugar Determination, *J Biol Chem* **100** 695-713 (May) 1933.

order to determine the efficiency of the metabolism of carbohydrate at night with the protamine insulin regimen, a blood sugar reading was made at 3 a m on November 12 and was found to be 35 mg per hundred cubic centimeters, although the patient at that time experienced no symptoms of hypoglycemia The adminis-

TABLE 1—Data for F Z (Case 1)*

Date	Sugar	Time of Examination					Administration of Insulin		
		7 a m	11 a m	3 p m	7 p m	3 a m	7 a m	Noon	6 p m
11/ 2/36	Blood	154	140	100	125		33 R	17 R	31 R
	Urine	0	0	0	0				
11/ 3/36	Blood	162	175	100	125		33 R	17 R	31 R
	Urine	0	+	0	0				
11/11/36	Blood	100	176	175	125	60	45 P		
	Urine	0	+	0	0				
11/12/36	Blood	135	195	135	180	35	45 P		
	Urine	0	0	0	0				
11/23/36	Blood	65	155	160	155	80	35 P at 5 30 p m		
	Urine	0	0	0	0				
11/24/36	Blood	70	155	150	125		35 P at 5 30 p m		
	Urine	0	0	0	0				
11/27/36	Blood	60	100	112	170		35 P at 7 p m		
	Urine	0	0	0	0				
11/28/36	Blood	90	155	135	115	100	35 P at 7 p m		
	Urine	0	0	0	0				

* In tables 1 to 12 R indicates regular insulin and P protamine insulin The values for blood sugar are given in milligrams per hundred cubic centimeters and those for insulin in units

TABLE 2—Data for M L (Case 2)

Date	Sugar	Time of Examination					Administration of Insulin		
		7 a m	11 a m	3 p m	7 p m	3 a m	7 a m	Noon	6 p m
12/20/36	Blood	112	80	160	135		21 R		20 R
	Urine	+	+	+	+				
12/22/36	Blood	110	100	135	160		21 R		20 R
	Urine	+	++	++	++				
1/ 7/37	Blood	60	75	165	185		30 P at 10 p m		
	Urine	++	+	0	0				
1/ 8/37	Blood	60	35	130	212		30 P at 10 p m		
	Urine	++	0	0	++				
1/ 9/37	Blood	45	75	120	200		30 P at 10 p m		
	Urine	+	0	+	+				
1/29/37	Blood	76	100	170	135	75	30 P		
	Urine	0	0	0	0				
1/30/37	Blood	80	155	200	125		30 P		
	Urine	+	+	++	+				
2/ 2/37	Blood	80	112	155	135	75	30 P		
	Urine	0	+	+	0				
2/ 3/37	Blood	80	55	195	125		30 P		
	Urine	0	0	0	0				
2/18/37	Blood	75	95	150	140	80	30 P		
	Urine	0	0	0	0				

tration of insulin was then advanced to 5 30 p m and finally to 7 p m Blood sugar readings were made at 3 a m on November 23 and again on November 28 and were found to be 80 and 100 mg per hundred cubic centimeters, respectively In this case regulation with protamine insulin was considered as successful, requiring only 58 per cent of the former number of units of regular insulin The number of doses was cut down from three to only one daily

CASE 2—M L, a man aged 66 years, weighing 72 Kg, was found to be suffering from diabetes when examined in the outpatient department and was admitted for regulation of the diet and the dosage of insulin. He was given a diet which consisted of 72 Gm of protein, 82 Gm of fat and 220 Gm of carbohydrate. The urine was free from sugar when insulin hydrochloride was given twice a day (21 units before breakfast and 20 units before supper). Blood sugar readings were made four times daily and were within physiologic limits. The patient was then given 30 units of protamine insulin at 10 p m. However, the values for sugar at night were high, while those obtained during fasting in the morning were low. The time of administration of the protamine insulin was then changed to 7 a m, and the blood sugar curves were satisfactory. Blood sugar readings

TABLE 3—Data for J B (Case 3)

Date	Sugar	Time of Examination				Administration of Insulin
		7 a m	11 a m	3 p m	7 p m	
7/ 9/36	Blood	125	135	160	165	45 P
	Urine	0	0	0	0	
7/10/36	Blood	125	135	140	170	45 P
	Urine	0	0	0	0	
7/11/36	Blood	150	160	175	175	45 P
	Urine	0	0	0	0	
7/12/36	Blood	135	140	100	125	45 P
	Urine	0	0	0	0	

TABLE 4—Data for W B (Case 4)

Date	Sugar	Time of Examination				Administration of Insulin		
		7 a m	11 a m	3 p m	7 p m	7 a m	Noon	6 p m
7/ 5/36	Blood	125	100	212	160	22 R	6 R	20 R
	Urine	0	0	0	0			
7/ 6/36	Blood	135	100	120	160	22 R	6 R	20 R
	Urine	0	0	0	0			
7/13/36	Blood	80	135	160	135	40 P		
	Urine	0	0	0	0			
7/14/36	Blood	112	185	160	135	40 P		
	Urine	0	0	0	0			
7/15/36	Blood	112	160	180	135	40 P		
	Urine	0	0	0	0			

were made at 3 a m for several successive nights and were always within normal limits. The patient was discharged when taking 30 units of protamine insulin once daily. Blood sugar readings were made on several occasions in the outpatient clinic and were always within normal limits. In this case, therefore, satisfactory regulation was secured with one dose of protamine insulin which was 75 per cent of the previous dose of regular insulin.

CASE 3—J B, a man aged 55 years, weighing 75 Kg, was known to have had diabetes for three years. With a diet of 75 Gm of protein, 135 Gm of fat and 160 Gm of carbohydrate he required three doses of regular insulin for satisfactory regulation (23 units in the morning, 6 units at noon and 23 units at night). Regulation was finally secured with 45 units of protamine insulin at 7 a m. Therefore satisfactory regulation was obtained with a single dose of protamine insulin, 72 per cent of the former dose of regular insulin being all that was required.

CASE 4—W B, a man aged 59 years, weighing 70 Kg, was given a diet consisting of 70 Gm of protein, 100 Gm of fat and 200 Gm of carbohydrate. Satisfactory regulation was obtained with three doses of old insulin (22 units in the morning, 6 units at noon and 20 units before the evening meal). Equally successful regulation was obtained with 40 units of protamine insulin given at 7 a m in one dose which constituted 83 per cent of the former dose of regular insulin.

CASE 5—M F was a woman aged 62 years, weighing 64 Kg. With a diet consisting of 64 Gm of protein, 98 Gm of fat and 196 Gm of carbohydrate, satisfactory regulation was obtained with 3 doses of old insulin (30 units in the

TABLE 5—Data for M F (Case 5)

Date	Sugar	Time of Examination					Administration of Insulin		
		7 a m	11 a m	3 p m	7 p m	3 a m	7 a m	Noon	3 p m
9/22/36	Blood	155	125	80	112		30 R	16 R	24 R
	Urine	0	0	0	0				
9/23/36	Blood	160	100	110	210		30 R	16 R	24 R
	Urine	0	0	0	0				
9/30/36	Blood	80	75	175	225	94	45 P		
	Urine	0	0	0	0				
10/ 3/36	Blood	100	110	120	100		45 P		
	Urine	0	0	0	0				
10/ 4/36	Blood	100	112	175	245		45 P		
	Urine	0	0	0	0				

TABLE 6—Data for G M (Case 6)

Date	Sugar	Time of Examination					Administration of Insulin		
		7 a m	11 a m	3 p m	7 p m	3 a m	7 a m	Noon	3 p m
2/10/37	Blood	160	90	135	185		25 R	10 R	20 R
	Urine	+	0	0	++				
2/15/37	Blood	75	135	200	150	48	40 P at 9 p m		
	Urine	+	+++	+++	+				
2/16/37	Blood	55	75	135	150		40 P at 9 p m		
	Urine	+	+	+	+				
3/ 2/37	Blood	120	235	135	160	112	35 P		
	Urine	0	+	0	0				
3/ 3/37	Blood	112	200	135	125	100	35 P		
	Urine	0	+++	++	0				

morning, 16 units at noon and 24 units in the evening). Fairly good regulation was obtained with 45 units of protamine insulin given in one dose at 7 a m. The blood sugar level at 7 p m, although a little higher than desirable, could easily have been lowered by giving a small dose of old insulin with the evening meal. This elevated level did not persist for any great length of time, since the 3 a m reading was 94 mg per hundred cubic centimeters.

In this case successful regulation was obtained with one dose of protamine insulin, whereas three doses of old insulin were previously necessary. This patient required only 77 per cent of the previous dose of old insulin given as protamine insulin, a saving of 23 per cent.

CASE 6—G M, aged 63 years, weighing 68 Kg, was known to have had diabetes for five years. With a diet containing 72 Gm of protein, 70 Gm of fat and 300 Gm of carbohydrate, satisfactory regulation was secured with three

doses of old insulin (28 units in the morning, 10 units at noon and 20 units in the evening) Protamine insulin was given in a single dose at 9 p m Blood sugar readings made four times daily showed fairly good control with one dose However, when the blood sugar reading was made at 3 a m, it was found to be 48 mg per hundred cubic centimeters, although the patient at that time showed no evidence of hypoglycemia The dose of insulin was lowered to 35 units and was given at 7 a m This produced a satisfactory regulation, and the blood sugar reading at 3 a m, was not unusually low

Regulation of the diabetic condition was successful, the number of doses was reduced from three to one and the dose of insulin was reduced by 40 per cent

The cases so far presented may be taken as typical examples of successful treatment In these cases definite advantages can be demonstrated in the use of protamine zinc insulin In the following cases, distinctly more difficult problems were presented

CASE 7—For C W, aged 66 years, weighing 62 Kg, the diagnosis of diabetes mellitus was made two weeks before her admission to the hospital She was given

TABLE 7—Data for G W (Case 7)

Date	Sugar	Time of Examination				3 a m	Administration of Insulin		
		7 a m	11 a m	3 p m	7 p m		7 a m	Noon	3 p m
12/14/36	Blood	85	80	160	160		20 R		16 R
	Urine	0	0	0	0				
12/15/36	Blood	85	90	160	170		20 R		16 R
	Urine	+	+	0	0				
1/ 9/37	Blood	90	185	270	260		25 P at 10 p m		
	Urine	++	+++	+++	+++				
2/ 1/37	Blood	112	160	212	200	50	30 P		
	Urine	++	+++	+++	++				
2/ 2/37	Blood	85	160	200	235		30 P		
	Urine	+++	++	++	++				

a diet consisting of 62 Gm of protein, 80 Gm of fat and 220 Gm of carbohydrate Regulation was obtained with two doses of regular insulin (20 units in the morning and 16 units in the evening)

After satisfactory regulation was obtained, protamine zinc insulin was given at 10 p m in a single dose of 25 units In the afternoon and evening the blood sugar levels were very high The dose of protamine insulin was raised to 30 units and was given at 7 a m Better blood sugar values were obtained during the day, however, at 3 a m the patient experienced a hypoglycemic reaction, and the blood sugar readings made the following day showed an unsatisfactory regulation of the carbohydrate metabolism, the urine showed 2 plus and 3 plus sugar

Successful regulation was not obtained with one dose of protamine zinc insulin We did not give this patient both types of insulin, since satisfactory regulation was obtained with two doses of old insulin and we considered it inadvisable to complicate the treatment of diabetes in this case by using two types of insulin

CASE 8—D W, a man aged 31 years, weighing 72 Kg, was known to have had diabetes for two years He was given a diet which consisted of 72 Gm of protein, 100 Gm of fat and 200 Gm of carbohydrate, with three doses of regular insulin (28 units at 7 a m, 12 units at noon and 26 units at 5 p m) Fairly good regulation was obtained, although in the morning during fasting the blood

sugar content was always high, the blood sugar values throughout the day were within normal limits. This patient was given 45 units of protamine insulin at 7 a m, as can be seen from the accompanying table, not only were the blood sugar peaks high, but the type of curve varied from day to day. Further evidence of the unsatisfactory regulation and lack of uniform action of protamine insulin in this case was the hypoglycemic reaction which occurred at 3 a m on Oct 4, 1936. The blood sugar value at that time was 44 mg per hundred cubic centimeters.

In this case satisfactory regulation was not obtained with one dose of protamine insulin.

TABLE 8—Data for D W (Case 8)

Date	Sugar	Time of Examination					Administration of Insulin		
		7 a m	11 a m	3 p m	7 p m	3 a m	7 a m	Noon	3 p m
9/29/36	Blood	250	160	135	115		28 R	12 R	26 R
	Urine	+++	+++	0	0				
9/30/36	Blood	255	120	90	80		23 R	12 R	26 R
	Urine	0	+	0	0				
10/ 3/36	Blood	75	90	125	235		45 P		
	Urine	++	++	0	++				
10/ 4/36	Blood	80	275	200	250	44	45 P		
	Urine	+	+++	+++	+++				
10/14/36	Blood	60	160	220	260		40 P		
	Urine	0	+	++	++				

TABLE 9—Data for E W (Case 9)

Date	Sugar	Time of Examination					Administration of Insulin			
		7 a m	11 a m	3 p m	7 p m	3 p m	7 a m	Noon	6 p m	10 p m
9/11/36	Blood	200	145	155	135		25 R	10 R	10 R	10 R
	Urine	+	+++	++	++					
9/12/36	Blood	235	105	85	190		25 R	10 R	10 R	10 R
	Urine	+	+	0	+					
10/ 9/36	Blood	60	220	180	190	35	30 P			
	Urine	0	+	0	0					
10/12/36	Blood	100	135	125	212	30	25 P			
	Urine	0	0	0	0					
10/14/36	Blood	155	250	190	178	44 at 9 p m	25 P			
	Urine	0	+++	+++	++					

CASE 9—E W, a man aged 24 years, weighing 76 Kg, was known to have had diabetes for two years. He was given a diet of 80 Gm of protein, 185 Gm of fat and 260 Gm of carbohydrate. Satisfactory regulation could not be obtained with less than four doses of regular insulin because of a labile type of blood sugar curve. The fourth dose was given at 10 p m with 200 cc of orange juice. Any attempt to lower the blood sugar level during fasting by raising the 10 p m dose of insulin caused a hypoglycemic reaction between the hours of 1 and 3 a m. However, with protamine zinc insulin the results were no better, the number of hypoglycemic reactions were more frequent with the new than with the old type of insulin. On one day it is seen that the blood sugar level fell from 212 mg to 30 mg per hundred cubic centimeters during a period of eight hours and from 178 to 44 mg per hundred cubic centimeters within two hours while the patient was receiving protamine insulin.

In this case the use of protamine insulin was not continued.

CASE 10—M H, a woman aged 70 years, weighing 70 Kg, was known to have had diabetes for fifteen years. She was given a diet containing 70 Gm of protein, 90 Gm of fat and 200 Gm of carbohydrate. Satisfactory regulation was obtained with three doses of old insulin (25 units in the morning, 8 units at noon and 10 units in the evening). She was then given 30 units of protamine insulin in one dose at 10 p m. A hypoglycemic reaction occurred at 3 a m. Giving the insulin at 7 a m eliminated the hypoglycemic reaction. However, the blood sugar curves

TABLE 10—Data for M H (Case 10)

Time of Examination										Administration of Insulin		
Date	Sugar	7 a m	11 a m	3 p m	7 p m	3 a m	7 a m	Noon	6 p m			
12/27/36	Blood	85	115	100	160		25 R	8 R	10 R			
	Urine	+	+	+	+							
12/28/36	Blood	85	112	90	150		25 R	8 R	10 R			
	Urine	+	+	++	+							
1/ 8/37	Blood	90	235	212	225	35	30 P at 10 p m					
	Urine	+	+++	+++	+++							
2/ 4/37	Blood	125	200	230	235	112	35 P					
	Urine	0	++	+++	+++							
2/ 8/37	Blood	100	175	250	175		35 P					
	Urine	0	++	+++	++							

TABLE 11—Data for R J (Case 11)

Date	Sugar	Time of Examination				Administration of Insulin				
		7 a m	11 a m	3 p m	7 p m	7 a m	Noon	6 p m	7 p m	10 p m
8/21/36	Blood	185	80	105	150	30 R	12 R	16 R		12 R
	Urine	0	0	0	0					
8/22/36	Blood	150	80	100	160	30 R	12 R	16 R		12 R
	Urine	0	0	0	0					
8/27/36	Blood	255	315	235	180	45 P				
	Urine	0	0	0	0					
9/ 7/36	Blood	300	375	250	225	35 P	15 P			
	Urine	+	+-++	++	+					
9/16/36	Blood	75	210	260	250	35 P			15 P	
	Urine	-	+	++++	+++					
9/28/36	Blood	60	150	275	275	40 P			15 P	
	Urine	0	-	+	++					
9/29/36	Blood	70	40	80	100	40 P			15 P	
	Urine	+-	0	0	0					
9/30/36	Blood	50	275	250	185	40 P			10 P	
	Urine	0	+-	+++	+++					
10/ 1/36	Blood	150	160	120	90	40 P			10 P	
	Urine	0	0	0	0					

were much inferior to those obtained when three doses of regular insulin were being given.

In this case, regulation was not as satisfactory with protamine insulin as with insulin hydrochloride.

CASE 11—R J, a man aged 51 years, weighing 79 Kg, was known to have had diabetes for six years. Diabetic coma occurred in 1935. This patient was given a diet consisting of 79 Gm of protein, 116 Gm of fat and 190 Gm of carbohydrate. Regulation was difficult with insulin hydrochloride but was finally obtained with four doses. The fourth dose was given at 10 p m with 200 cc of orange juice. Treatment was then started with 45 units of protamine insulin given in a single dose at 7 a m. This was unsatisfactory. The effect of splitting the dose of

protamine insulin in two was next tried Thirty-five units was given at 7 a m and fifteen units at noon This did not improve the blood sugar curve, and the time for the second dose was changed to 7 p m, with still less satisfactory results As can be readily seen from the accompanying table, the blood sugar curves varied greatly from day to day

In this case, satisfactory regulation was not obtained with one or two doses of protamine insulin

CASE 12—M S, a woman aged 66 years, weighing 62 Kg, was known to have had diabetes for six years and had experienced diabetic coma on three separate occasions She received a diet which consisted of 62 Gm of protein, 90 Gm of fat and 190 Gm of carbohydrate Regular insulin was given three times daily (32 units before breakfast, 10 units before the noon meal, 34 units before the evening meal) The blood sugar value in the morning during fasting was very

TABLE 12—Data for M S (Case 12)

Date	Sugar	Time of Examination					Administration of Insulin		
		7 a m	11 a m	3 p m	7 p m	3 a m	7 a m	Noon	6 p m
7/19/36	Blood	300	200	100	125		32 R	10 R	34 R
	Urine	0	++	0	0				
7/20/36	Blood	325	125	75	135		32 R	10 R	34 R
	Urine	0	++	0	0				
7/24/36	Blood	200	275	285	235	40	55 P		
	Urine	0	++++	++	0				
7/25/36	Blood	235	135	35	115		35 P		
	Urine	0	++++	0	0				
8/18/36	Blood	75	250	350	235		35 P		15 P
	Urine	0	+	++++	+++				
8/24/36	Blood	150	200	190	125		33 P		15 P
	Urine	0	+	++	0				
8/25/36	Blood	125	225	225	175		33 P		15 P
	Urine	0	+++	++	0				
8/27/36	Blood	112	135	230	235		35 P	15 P	
	Urine	++	0	+	+				
9/28/36	Blood	50	160	160	165		35 P	15 P	
	Urine	0	0	0	+				
9/29/36	Blood	35	125	185	270		35 P	15 P	
	Urine	0	0	0	++				

high, but the values during the day were within normal limits She was given 55 units of protamine insulin at 7 a m On the fourth day of this regimen, she had a severe hypoglycemic reaction at 5 a m The blood sugar content was 40 mg per hundred cubic centimeters at that time The dose of protamine insulin was then divided in two, 35 units was given at 7 a m and 15 units at 7 p m When this was found to be unsatisfactory, the effect of giving the second dose before the noon meal instead of at 7 p m was tried The blood sugar curves were found to be satisfactory, and the patient was discharged, receiving 35 units of protamine insulin at 7 a m and 15 units at noon She returned two weeks later in a state of severe hypoglycemic shock This condition was relieved by the administration of dextrose intravenously Thinking that the hypoglycemic reaction had been due to improper dietary regulation on the part of the patient, we continued to give her protamine insulin as on the day of her previous discharge The blood sugar value during fasting on two consecutive mornings was found to be dangerously low, so that the use of two doses of protamine insulin had to be discontinued

In this case regulation was not satisfactory with one or two doses of protamine zinc insulin

COMMENT

Of the present series of 12 patients with diabetes mellitus chosen at random, 6, who had previously required two or three doses of regular insulin, showed satisfactory regulation with one dose of protamine zinc insulin. Consequently, a saving of from 17 to 42 per cent was noted when protamine zinc insulin was substituted for the regular insulin hydrochloride in these cases. Five of these patients did well when the protamine insulin was given at 7 a m, while in one case regulation was obtained only by the administration of protamine insulin at 7 p m (table 1). In the great majority of cases the lowest blood sugar level for the twenty-four hour period was found to occur twenty hours after the injection when the protamine insulin was given at 7 a m and five hours later when it was given at 10 p m. The only exception to this rule was noted in case 1, the low point was observed after twelve hours when the protamine insulin was given at 7 p m (table 1). It was our constant observation that if protamine insulin given in a single dose was unsuccessful in producing satisfactory blood sugar curves, splitting the dose in two frequently caused even greater variations in the blood sugar curves than did one dose (tables 11 and 12).

When the action of regular insulin is studied it is always observed that a given amount of insulin will cause a fairly constant drop in the blood sugar level provided the diet remains unchanged and no infectious process is present, so that if the blood sugar reading is taken at the same time on several consecutive days, it will not vary to any great extent from the reading taken at the same time the day previously. Also the type of curve obtained when two or three doses of regular insulin are given will not vary to any great extent from day to day even in cases of more severe diabetes. This observation also holds true for the patients successfully regulated with protamine insulin. However, the patients who were unsuccessfully treated with one or two doses of protamine insulin showed blood sugar curves which varied greatly from day to day (tables 8, 9, 11 and 12). This observation suggests that the action of protamine insulin in these cases is not uniform. This may be due to a difference in the rate of absorption or to factors associated with the reactivation of the protamine insulin. For example, in table 9 it is seen that on the third day there occurred a fall in blood sugar content from 178 to 44 mg per hundred cubic centimeters within a period of two hours.

The inability of protamine insulin to prevent abnormally high elevations of the blood sugar level after meals is clearly demonstrated in all the cases in which treatment was unsuccessful and to a lesser degree in 2 of the cases in which treatment was successful (tables 5 to 12). The blood sugar content in these cases will be noted to be much higher,

more frequently in the absorptive state with protamine than with the regular insulin. This is to be expected, because with protamine insulin the rate of absorption from the subcutaneous tissue is gradual and therefore there is only a small amount of insulin available for immediate use at any given time to cope with a sudden increase of sugar in the blood, such as occurs after meals, and for that reason a higher blood sugar content will be noted during the hours following meals when protamine is used. In this respect a rapidly acting insulin given before meals is more physiologic in its action than a slowly acting insulin.

In further support of the conclusion that protamine is absorbed slowly and that the fall in blood sugar content is gradual is the observation reported by various investigators^{2a} that many patients may show hypoglycemia without experiencing the symptoms which are associated with it. We have corroborated this observation many times, particularly when we have had occasion to make the blood sugar reading at 3 a. m. At that time the blood sugar level is frequently found to be below 50 mg per hundred cubic centimeters, but the patient does not have symptoms of hypoglycemia. This occurrence of "symptomless hypoglycemia" with slowly acting insulin we consider a great disadvantage which may prove to be quite harmful. It is well known that an anginal attack may be brought on by a low blood sugar content, particularly in diabetic patients with arteriosclerosis.⁵ Wilder⁶ has recently reported that if in dogs the blood sugar content is kept at a low level for a certain length of time, the attempt to raise the content by the intravenous administration of dextrose frequently results in death of the animal. Somogyi⁷ has presented evidence to show that after hypoglycemia there occurs a compensatory period of hyperglycemia in the diabetic patient, with an increased degree of glycosuria as well as a reduced tolerance for sugar. We therefore believe that it is better for a patient to have a moderately elevated blood sugar level during the night than a low one. Since with the use of protamine insulin the low point usually falls around 3 a. m. and hypoglycemia may occur without symptoms, the importance of determining the blood sugar level at this hour is at once evident. When employing protamine insulin we found that the principles commonly followed for treatment with regular insulin had to be modified. Whereas with regular insulin the highest blood sugar value obtained during the twenty-four hour period is taken

5 Parsonnet, A. E., and Hyman, A. S. Insulin Angina, *Ann Int Med* **4** 1247-1256 (April) 1931

6 Wilder, R. M. Clinical Investigations of Insulins with Prolonged Activity, *Ann Int Med* **11** 13-30 (July) 1937

7 Somogyi, M. Hyperglycemic Response to Hypoglycemia in Diabetic and in Healthy Individuals, *Proc Soc Exptl Biol & Med* **38** 51-55 (Feb) 1938

as the important figure and for that reason the morning value during fasting is the chief criterion of the state of regulation of the diabetes, when protamine insulin is used the low point also has to be watched. For that reason a 3 a m estimation of the blood sugar content is to be recommended. This, of course, is difficult to secure unless the patient is in a hospital.

Examination of the charts, as already pointed out, reveals the fact that if protamine zinc insulin is administered at 7 a m, the lowest blood sugar value in the twenty-four hour period will be obtained in nearly all cases after twenty hours. On the other hand, if the injection of insulin is made at 10 p m, the low point will in most cases occur after five hours. This fact makes the administration of protamine insulin at night unsuitable in most cases, since the greatest effect of protamine insulin would be desirable after the elapse of about ten hours, when breakfast is due (this occurred in only 1 of our series of cases, table 1). Why the low point should occur after five hours when protamine insulin is given at 10 p m is a matter of speculation. One would expect that since the effect of protamine insulin is continuous, the fall in blood sugar level ought to continue well after 3 a m, so that the 7 a m value would be lower than the 3 a m value. However, as can be seen from tables 2, 5 and 6, such is not the case. After this low point, if a hypoglycemic reaction does not occur the blood sugar level will rise, so that the 7 a m value will be higher than the 3 a m value. A possible explanation is that the falling blood sugar level causes stimulation of the adrenal glands, with consequent liberation of glycogen from the liver so that the blood sugar value will rise once this critical level is reached. When this compensation does not take place, a hypoglycemic reaction will occur.

SUMMARY

Fluctuations in the blood sugar values for 12 diabetic patients who were first treated with regular insulin and then with protamine zinc insulin are presented.

In 50 per cent of our cases, regulation was successful with one daily injection of protamine insulin, and the total requirement for insulin was reduced from 42 to 17 per cent.

In 50 per cent of the cases, satisfactory regulation could not be obtained with either one or two doses of protamine insulin.

In agreement with the reports of other investigators we found that protamine insulin had a more gradual and prolonged lowering effect on the blood sugar content than did regular insulin hydrochloride.

In 5 of our cases in which treatment with protamine insulin was successful, the insulin was administered at 7 a m. In 1 case regulation was obtained when the protamine insulin was given at 7 p m.

The importance of determining the blood sugar value at 3 a m when regulation has apparently been obtained with protamine insulin is pointed out

The renal threshold for dextrose may vary for an individual from time to time

CONCLUSION

In our series of cases the lowest blood sugar level during the twenty-four hour period was found to occur (*a*) after twenty hours when the protamine insulin was injected at 7 a m and (*b*) after five hours and in 1 case after twelve hours when it was injected at 10 p m

In view of the uncertainty regarding the occurrence of the lowest blood sugar level after the injection of protamine insulin, it is obvious that the use of this material by physicians for the treatment of patients in their homes is likely to be associated with more frequent low blood sugar levels than when regular insulin hydrochloride is used

Since many believe that hypoglycemia is more dangerous to the patient's well-being and therefore more to be avoided than moderate hyperglycemia, a distinct question is raised regarding the selection of patients amenable to treatment with protamine insulin

DIFFUSE ARTERIAL DISEASE WITH HYPERTENSION

TWO UNUSUAL CASES OF CONTRASTING TYPES

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For the last fifteen years a group at the Mayo Clinic have been interested in the difficult problem of diffuse arterial disease with hypertension. Periodically an unusual case of this disease is encountered which upsets prevailing ideas and compels an alteration of views with regard to the general problem. In this paper we wish to describe and discuss 2 such cases. They are undoubtedly extreme examples, but they present interesting features that are not altogether typical and accentuate important points which may add to the knowledge of the group of more general examples. The patients were both physicians in the prime of life, and diffuse arterial disease was the cause of death in both cases. The clinical course and the retinal and pathologic data will be stressed in this report.

CASE 1—On May 15, 1936, the first patient, a physician 46 years of age, came to the clinic complaining of profound fatigue, pains in the extremities, irregularity of the heart beat, polyuria and nocturia. The family history was irrelevant. He had diphtheria at the age of 6 years and mumps at 13, followed by orchitis on the right side. He had gonorrheal urethritis at 19. His tonsils were removed when he was 24, and he underwent appendectomy when he was 31.

He attributed his current illness to an incident which occurred in February, three months before his visit to the clinic. When returning from a midnight visit to a patient, he suffered severe exposure when his car stalled and he had to crawl under it to make some repairs, the temperature being 24 F below zero. Four days later chilly sensations, fever and backache in the lumbar region developed. Fever continued daily, the temperature mounting to 103 or 104 F daily for two weeks. Later he became progressively more fatigued. In March nocturia appeared, and often he passed 1,500 to 2,000 cc of urine during the night. In April he noticed that his heart beat was irregular. He continued to practice medicine, however, in spite of these symptoms.

On examination at the clinic on May 15 his blood pressure in millimeters of mercury was 165 systolic and 120 diastolic (fig 1). He weighed 195 pounds.

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(88.6 Kg) Vision in the right eye was 6/7, in the left, 6/6 The ocular fundi were normal There were occasional extrasystoles, but no other cardiac abnormality was detected A single specimen of urine contained no albumin or casts, and only

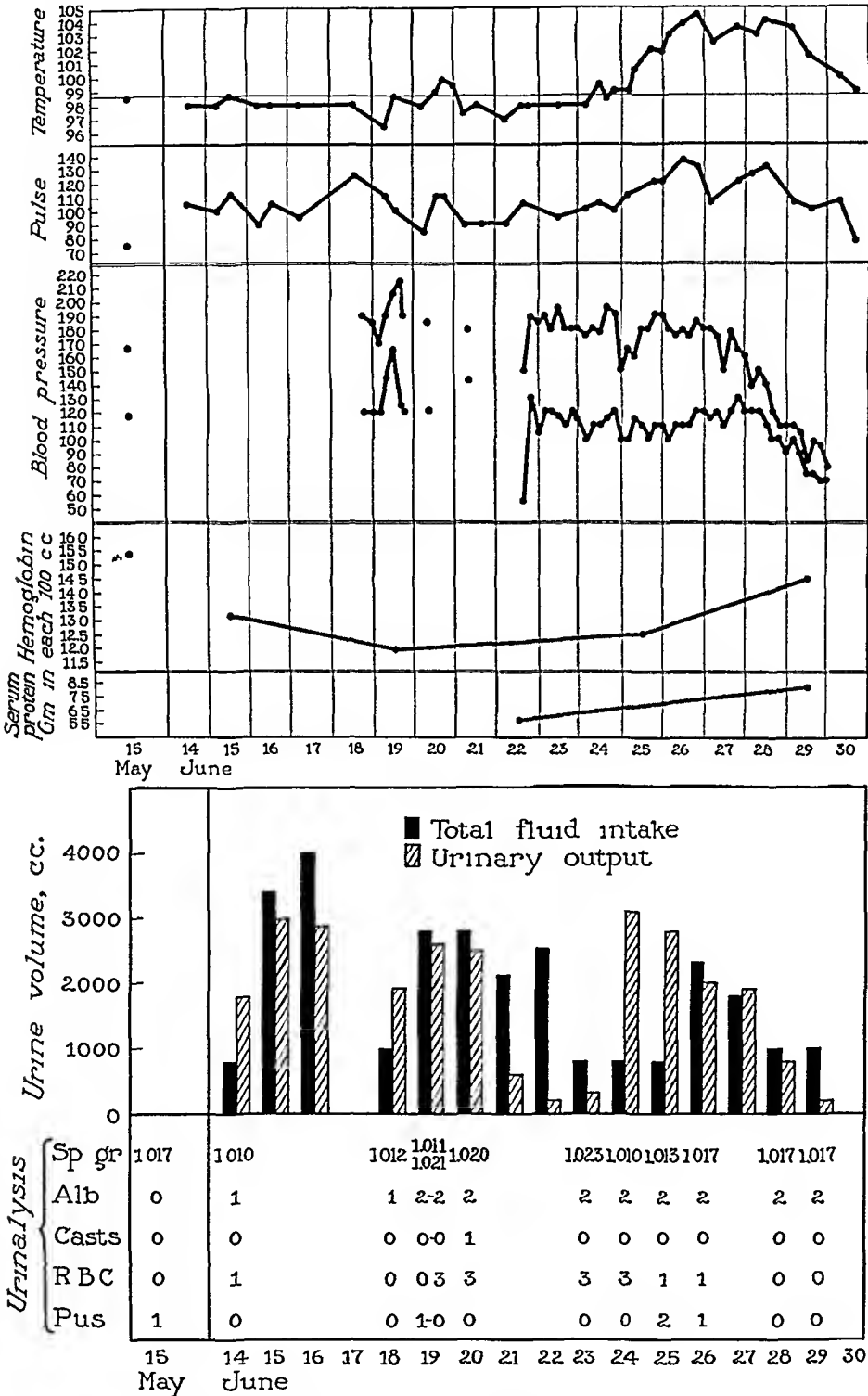


Fig 1 (case 1) —Charts showing the variation in temperature, pulse rate and blood pressure, in the concentrations of hemoglobin and protein in the blood and serum, in intake of fluid and volume of urine and in results of urinalyses

6 pus cells were present per high power field. The blood urea content was 26 mg per hundred cubic centimeters (table 1). Roentgenograms of the thorax and of the region of the kidneys, ureters and bladder were normal. No definite diagnosis was established, and the patient was sent home to rest.

One week after the patient left the clinic he began to vomit whenever he ate, and often he strained and tried to vomit even when his stomach was empty. He had severe headaches once or twice weekly and said he felt as though his

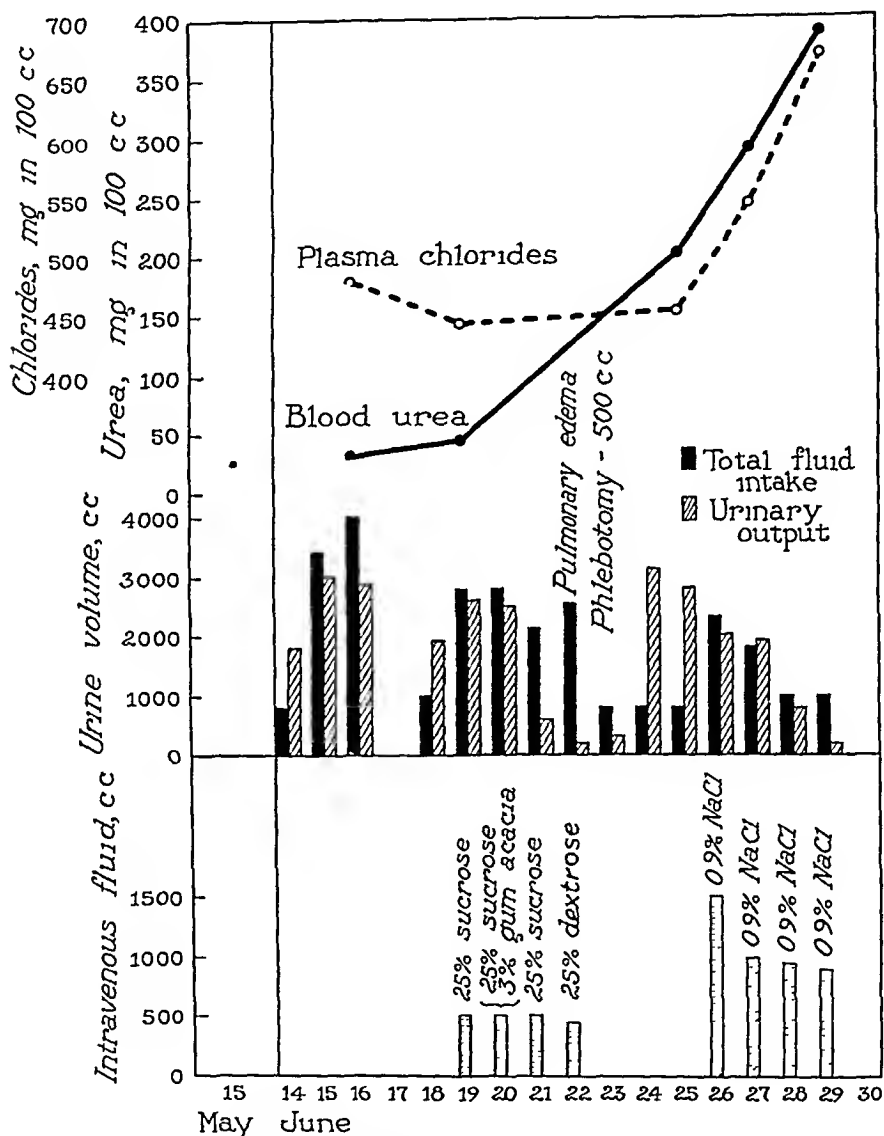


Fig 2 (case 1) —Chart showing variations in blood urea and plasma chloride values in relation to intake of fluid and volume of urine

head were in a vise. He would sometimes drop off to sleep while consulting with a patient. He had spells of severe crying. Pains in the extremities became marked and "drove him wild." One week before his second visit he awakened to find that his vision was dim, and subsequently he was able to read only with great difficulty.

He returned to the clinic on June 14, 1936. While making a reexamination, Dr. F. A. Willius noted that the patient's heart was overactive. The heart rate

TABLE 1—*Data on the Blood (Case 1)*

Date, 1936	First Visit		Second Visit							
	5/15	5/16	6/15	6/16	6/19	6/22	6/25	6/26	6/27	6/29
Hemoglobin, Gm per 100 cc	15.4		13.3		11.9		12.5			14.5
Erythrocytes, millions per cu mm	4.05		3.59		4.09		3.37			
Leukocytes, per cu mm	8,900		15,200		11,000		22,000	25,100		
Lymphocytes, per cent	9		10.5		8.5			8		
Monocytes, per cent	7.5		7.5		5			4.5		
Neutrophils, per cent	80.5		80		86			86.5		
Eosinophils, per cent	2.5		1.5		0.5					
Basophils, per cent	0.5		0.5							
Myelocytes, per cent								1		
Normoblasts, per cent								1.5		
Morphologic appearance of blood smear	No features of pernicious anemia					Toxic, 2*		Toxic, 3*		
Urea, mg per 100 cc		26		32	44		202		291	390
Creatinine, mg per 100 cc							8.8		8.4	8.8
Serum sulfate, mg per 100 cc					4.2					
Sugar, mg per 100 cc		109		102						
Plasma chloride (as sodium chloride), mg per 100 cc				481	445		455		554	669
Carbon dioxide combining power of plasma, volumes per cent					70		53		57	56
Urea clearance, cc per minute					58					
Volume of urine, cc per hour					255					
Sulfate clearance, cc per minute					55					
Plasma cholesterol, mg per 100 cc						151				
Serum calcium, mg per 100 cc						8				
Serum protein, Gm per 100 cc						5.6				8.2
Albumin globulin ratio						1.12				
Serum nonprotein nitrogen, mg per 100 cc						67				
Serum sodium, mg per 100 cc						313	313			414
Serum potassium, mg per 100 cc						12.8	17.6			17.9
Hematocrit reading, %							36			

* Grade

was 108 per minute, and the tones were tumultuous. There was marked accentuation of the aortic second sound without apparent enlargement of the heart. Dr Willius suggested that a vasospastic type of hypertension might be developing. A roentgenogram of the stomach was made to rule out any local lesion as a possible explanation for the vomiting, it revealed no abnormality. Routine urinalysis showed the presence of a trace of protein and a few erythrocytes.

The patient was admitted to the hospital on June 18. At that time there was no dyspnea, and only slight cyanosis was noted. He looked pale. There was slight puffiness of the eyelids, which he believed was natural to him. His vision was 6/15 in the right eye and 6/10 in the left. He was able to read Jaeger test type 050 with glasses. The visual fields were roughly normal. The pupils reacted to light and in accommodation. Ophthalmoscopic examination revealed localized and generalized narrowing of the retinal arterioles (graded 1 to 2 in the larger and 3 in the smaller ones) without visible evidences of sclerosis, edema of the optic disks, diffuse edema of the peripapillary retina, scattered cotton-wool patches and hemorrhages, a few yellow foci in the choroid and, in the right eye, extensive subretinal edema which had produced detachment of the lower part of the retina. This picture resembled that seen at times in eclamptic toxemia of pregnancy and was interpreted as indicating acute angiospastic retinitis¹. It was thought at this time that the yellow foci in the choroid might represent localized spasms in the choroid arteries, but in view of the histologic observations they were probably due to hyaline infiltration in the walls of the arteries of the choroid. The patient's breath was not uremic, and his lungs were clear. There was a systolic heave over the entire precordium, and the left nipple rose and fell with each heart beat. The cardiac borders extended 3 cm to the right and 11 cm to the left of the midsternal line. The cardiac action was regular. There was a short aortic systolic murmur, followed by an accentuated second sound (accentuation, grade 2 plus). The abdomen was soft on palpation. The liver could not be felt. The peripheral sclerosis was graded 3 and was of the rubbery type. The patient had no edema. There was no gross neurologic abnormality, Kernig's sign and rigidity of the neck were absent. There was, however, marked generalized muscular tenderness, particularly in the biceps brachii and in the supraspinatus and quadriceps extensor groups.

On June 20, two days later, urinalysis revealed the presence of albumin, grade 2, erythrocytes, grade 3, and a few hyaline casts (fig 1). The arterioles of the retina showed increased generalized and localized spasm. The edema had receded to some extent from the upper portion of the retina, but more cotton-wool patches were present, and the lower part of the retina in each eye was definitely detached as a result of the subretinal edema. Culture of the blood made on June 21 was sterile. On that same day examination of the capillaries of the nailfold by the technic of Lombard revealed fairly long loops in which both limbs were decreased in caliber, the flow was markedly increased and of the spurting type, but the number of loops in each area was about normal.

On June 22 the patient was not clear mentally, and the urinary output for the preceding twenty-four hours was only 600 cc (figs 1 and 2). It was discovered that the liver had descended to 9 cm below the right costal margin in the mid-clavicular line. At 1:30 p m on the same day an intravenous infusion of 25 per cent solution of dextrose was being given, 450 cc had run into the vein when

¹ Wagener, H. P., Barker, N. W., and Burke, C. F. Acute Angiospastic Retinitis. Occurrence in Cases of Severe Hypertension and Renal Disease, *Am J M Sc* **185**:517-529 (April) 1933.

the patient suddenly became cyanosed and had to sit up in bed for breath. He coughed up frothy blood-stained sputum. Bubbling rales were heard over the entire pulmonary field.

On June 23 at 8 a. m. the patient seemed more irritable than usual. His respirations were periodic, but no actual apneic periods were noted. The pulse rate varied from moment to moment in a remarkable manner, slowing to 64 beats and then, within a few seconds, increasing to 104 beats per minute. These variations had no exact relation to respiratory changes. The total urinary output had dropped in the previous twenty-four hours to only 180 cc (fig 1). On percussion the area of cardiac dulness was found to be definitely widened, measuring 35 cm to the right and 13 cm to the left of the midsternal line. No rales or other abnormal signs could be discovered on examination of the thorax, although a roentgenogram showed diffuse opaque patches throughout both lungs (fig 3). The cerebrospinal fluid obtained at 11 a. m. was clear, the initial subarachnoid pressure was 30 cm of water and the response to the Queckenstedt test was prompt and satisfactory. At 3:30 p. m. phlebotomy was performed, and 500 cc of blood was removed.

On June 24 at 8 a. m. the patient seemed slightly drowsy but answered questions intelligently. There was some twitching of the arms. The neck was not stiff, and Kernig's sign was not present. On this day reexamination of the capillaries of the nailfold showed an increased number of loops in each field, otherwise there was no change, and the capillary blood was not cyanotic.

On June 25 the patient's temperature rose to 102 F (fig 1). The electrocardiographic tracings made on June 19 and 23 showed no characteristic or distinct abnormalities. A culture was made of a specimen of urine obtained by catheter on that day and was found to be sterile.

On June 26 at 8 a. m. the patient was in a peculiar restless semicomatose state. He was able to obey simple commands. There was no other gross neurologic abnormality. His respirations continued to be periodic, and, in addition, there were apneic periods lasting as long as ten seconds. Chemical analysis of the blood revealed marked renal insufficiency (table 1 and fig 2).

On June 27 at 8 a. m. the cerebrospinal fluid was clear, and the initial subarachnoid pressure was 2 cm of water. The apneic periods were as long as fifteen seconds. No evidence of meningeal irritation was present, and no organisms were seen in the stained smears of cerebrospinal fluid. Ophthalmoscopic examination revealed an increase in the edema of the retina. The detached portions of the retina were elevated about 8 diopters. The disks were definitely edematous, the elevation measuring 2 diopters. Cotton-wool patches and hemorrhagic areas were quite numerous. Punctate areas of exudate in the macular region of the edematous retina indicated the commencing formation of star figures. A roentgenogram of the thorax revealed clear pulmonary fields (fig 3).

On June 28 at 8 a. m. the patient was throwing his arms and legs around in bed. There was no cyanosis. The pupils were dilated. Examination of the blood indicated further impairment of renal function (table 1 and fig 2).

On June 29 the heart had decreased in size. On percussion its borders were found to extend 3 cm to the right and 10.5 cm to the left of the midsternal line. The heart sounds were barely audible, and there was a to and fro leathery murmur in the third interspace to the left of the sternum. The cardiovascular findings were those of shock. Culture of the blood made on this day was sterile. The patient died at 7:20 a. m. on June 30.

The following note was made by Dr. A. R. Barnes on a series of electrocardiographic tracings taken on May 15 and on June 19, 23 and 29. "The initial elec-

trocardiogram taken on May 15 was within normal limits. The tracing taken at the time of the second entry, June 19, showed a decreased voltage in all leads. The tracing on June 23 showed improved voltage of the T wave of lead II and a normal fourth lead. On the morning of June 29 there appeared in the tracing a Q wave in lead III, the T wave in the same lead was inverted and T_2 became diphasic. The Q wave in the fourth lead showed less excursion, and the T wave was definitely shallower. In the tracing taken in the evening the T wave was inverted in leads II and III, a Q_3 was present. The amplitude of QR_4 was

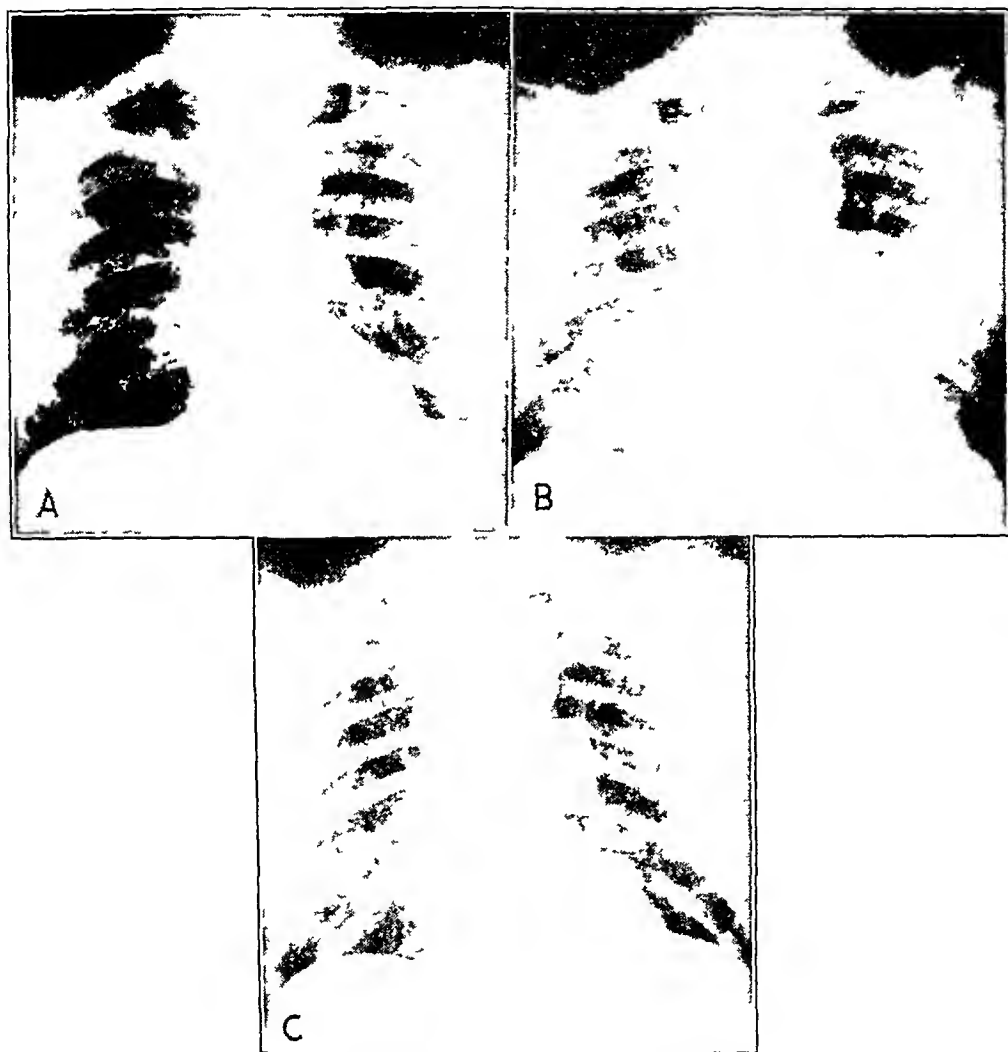


Fig 3 (case 1)—Teleroentgenograms of the thorax taken on May 15 (A), June 23 (B) and June 27, 1936 (C). The first and last ones (A and C) are essentially the same. The one taken on June 23 (B) shows areas of congestion in both lungs.

reduced, and the T wave in lead IV was shallow or diphasic. There was nothing in these tracings suggesting either hypertension or acute coronary occlusion."

Necropsy Observations—The outstanding pathologic changes in the vascular system were in the smaller arteries which measured approximately 100 to 500 microns in diameter and in the arterioles which measured from approximately 30 to 100 microns in diameter. The smaller arteries in many organs were diffusely inflamed, and this inflammation was seen in various stages of development. In

some instances the walls of the vessels were infiltrated with moderate numbers of lymphocytes, and a few lymphocytes had collected about the external coat. Where the process was more advanced the inflammatory reaction was more pronounced in the wall of the artery, in places leading almost to complete destruction of the muscular coat. In some vessels the subendothelial tissues were particularly invaded with inflammatory cells and were markedly thickened. This thickening occurred at the expense of the lumen, and in many instances the subendothelial inflammation had entirely obliterated it. In these vessels the Weigert stain for elastin showed the internal elastic lamina to be apparently displaced toward the periphery, so that the muscle existed merely as a thin band about the greatly thickened subendothelial layer. Where inflammation was most advanced, all the coats of the artery were destroyed, and the wall of the vessel was converted into a mass of scar tissue.

The arterioles showed changes characteristic of hypertension. The walls were thickened generally, with a resulting diminution in the ratio of the thickness of the wall to the diameter of the lumen. Thickening of the wall was due in part to an increased number of muscle cells in the medial coat. In some instances the endothelial lining appeared to be "piled up." About many arterioles there was a small region of fibrosis, and some had perivascular collections of lymphocytes. Differential stains did not show any increase in fibrous tissue in the arteriolar walls, and signs of degeneration were in general absent. Occlusion of the arterioles was not common, and the stain for elastin did not show any marked change in the elastic lamina.

The changes described in the arteries were seen in the choroid layer of the eyes, in the kidneys, heart, liver, spleen, pancreas, fibrous capsules of the adrenal glands and prostate gland and in both the large and the small bowel. The arteriolar changes described were also present in these organs, and in addition they were present in the voluntary muscles. The vessels of the lung were not markedly altered (figs 4 to 6).

The right kidney weighed 160 Gm and the left 178 Gm. The capsules stripped easily. There were multiple elevated yellowish areas of recent infarction on the renal surfaces, varying from a few millimeters to 1 cm in diameter. Microscopically, thrombosed vessels were seen leading to the infarcts. Many glomeruli in noninfarcted regions were intact. There were some areas of parenchymatous degeneration of the tubules, but these were not widespread. Congo red stain did not reveal the presence of amyloid in the kidney or its vessels.

The heart weighed 460 Gm. There was sclerosis, grade 2, of the coronary arteries, but none was occluded. The left ventricle was dilated, grade 3. On microscopic examination small areas could be seen beneath the epicardial covering on the ventral aspect of the intraventricular septum, in which the cardiac muscle had been completely destroyed and replaced by loose fibrous tissue. These areas were probably small infarcts. Elsewhere the myocardium appeared to be normal. The scarlet red stain demonstrated fatty degeneration of some of the muscle fibers of the heart. Congo red stain did not reveal the presence of any amyloid.

The spleen weighed 191 Gm, and there were several small nodules of chronic tuberculosis scattered about its surface. The liver weighed 913 Gm, and numerous nodules of chronic active tuberculosis were present on its surface.

There was a small area of atelectasis in the middle of the lower lobe of the right lung, and evidence of chronic tuberculosis was seen in the lymph nodes of the hilus of the right lung. There were a few nodules of healed tuberculosis in the subpleural region of the upper lobe of the right lung.



Fig 4 (case 1) —A, photomicrograph of the heart showing subpericardial fibrosis. A small artery shows diffuse inflammatory changes. Hematoxylin and eosin stain, $\times 85$. B, liver. An arteriole shows periarteritis with thickening of the media. Hematoxylin and eosin stain, $\times 750$. C, pancreas. A small artery shows moderate inflammatory changes in the intima and media. Weigert stain for elastic tissue, $\times 115$.

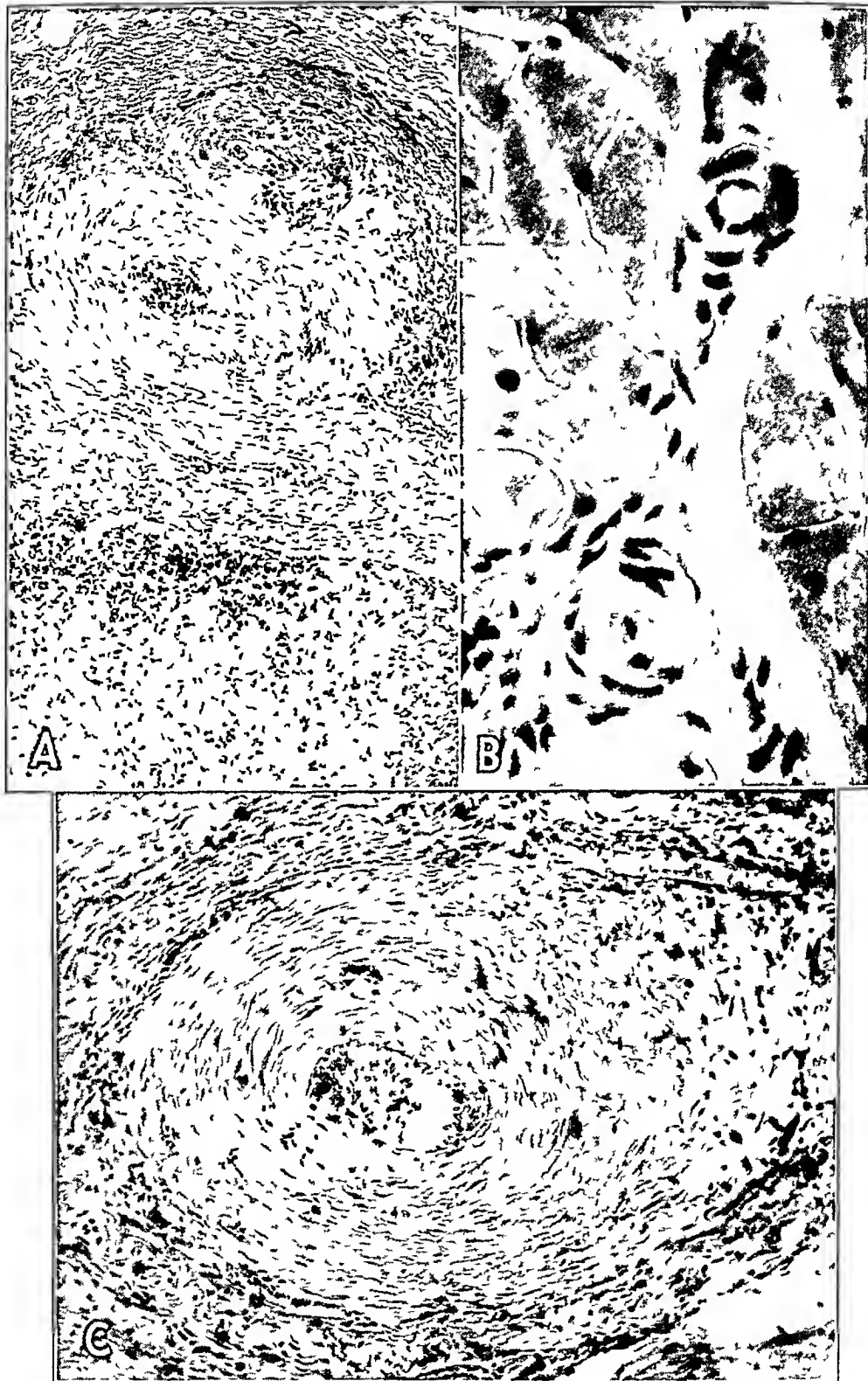


Fig 5 (case 1) —*A*, photomicrograph of the fibrous capsule of the adrenal gland. Small arteries show replacement of all the coats by an inflammatory process. Hematoxylin and eosin stain, $\times 100$. *B*, pectoralis major muscle. The arterioles show proliferation of the intimal endothelium, thickening of the media, periarteriolar fibrosis and an increased number of lymphocytes. Hematoxylin and eosin stain, $\times 500$. *C*, kidney. A small artery shows mild periarteritis with fibrosis and thickening of the wall and narrowing of the lumen. Hematoxylin and eosin stain, $\times 185$.

The pancreas weighed 100 Gm, and there was a small area of chronic tuberculosis in the tail. The aorta showed atherosclerosis, grade 2.

In each ocular bulb there were numerous small flame-shaped hemorrhages, and each retina was seen to be detached from the choroid by serofibrinous exudation. Histologically the most interesting and the only unusual finding was in the medium-sized arteries of the choroid. In approximately 20 per cent of these arteries, hyalin-like necrosis of the media was present. The hyalin-like material was fragmented and clumped into small masses, simulating the appearance in amyloid disease. It stained bright pink with eosin and did not contain any nuclei. There was no proliferation of the intima. There was slight proliferation of the adventitial connective tissue (fig 6).

The vessels of the brain were normal except for slight thickening of the walls of the arterioles. In the vessels of the pia-arachnoid, at the bottom of some of the sulci, there were chronic inflammatory changes.

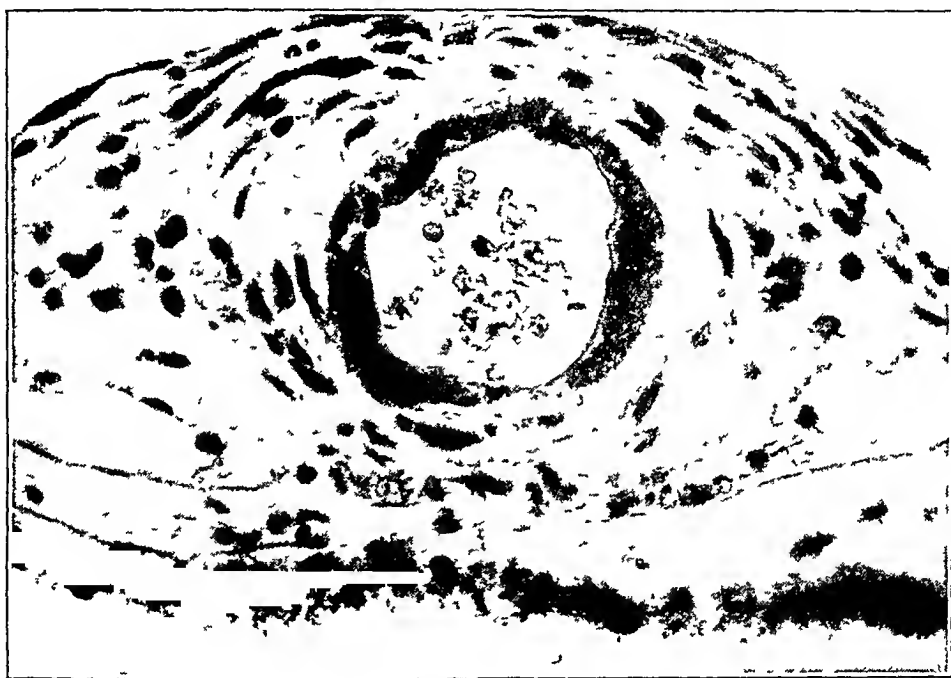


Fig 6 (case 1)—A small artery in the choroid layer of the eye. The lumen of the vessel is irregular. The inner portion of the media shows necrosis and irregular clumps of hyalin-like material. The adventitial connective tissue shows slight proliferation. Hematoxylin and eosin stain, the tissue being embedded in photoxylol, $\times 435$.

CASE 2²—This patient, also a physician, was 49 years of age when he first came to the clinic, on Oct 5, 1931. According to the family history, his father died of pernicious anemia at the age of 62 and his mother of hypertensive cardiovascular disease with angina pectoris at the age of 72. The patient had 3 children, living and well. He had diphtheria and scarlet fever in childhood, typhoid at the age of 17, followed by phlebitis of the left leg, and influenza during the epidemic of 1918. He underwent appendectomy at the age of 27 and tonsillectomy at the age of 39.

² Dr Lester J Palmer, of Seattle, supplied many of the details of the history and course in this case and many of the pathologic data.

When the patient was 46 years old, three years before his first visit to the clinic, he began to notice occasional momentary attacks of precordial distress and slight dyspnea when he ran or when he climbed a hill. These attacks were not definitely painful, and there was no projection of the distress. Both distress and dyspnea rapidly subsided with rest. In February 1930 a competent clinician examined the patient and found "no marked abnormality of the heart, blood pressure or electrocardiogram." In September 1930 the blood pressure was again found to be normal. In September 1931 hypertension was discovered during a routine examination.

On examination at the clinic the patient weighed 210 pounds (95.4 Kg) clothed. He was 5 feet and 11 inches (180 cm) in height. A single determination of the blood pressure was 170 systolic and 120 diastolic. He was well nourished, and there was no anemia or edema. The pupillary reflexes were normal. The lungs were clear. The heart measured 3.5 cm to the right and 12 cm to the left of the midsternal line, its action was regular and there were no murmurs. There was slight accentuation of the aortic second sound, and a slight systolic heave was visible over the precordium. Abdominal and rectal examinations revealed no abnormality, and there was no gross neurologic abnormality. On palpation only slight sclerosis of the peripheral arteries was found. Vision was 6/7 in the right eye and 6/6 in the left. Examination of the ocular fundi revealed mild sclerosis (grade 1) of the hypertensive type in the retinal arterioles.

The urine at this time contained no albumin or casts. There was no anemia, the hemoglobin value being 17.5 Gm per hundred cubic centimeters, the erythrocyte count 4,920,000 and the leukocyte count 6,800 per cubic millimeter of blood. The value for blood urea was 22 mg and that for serum sulfates 5.7 Gm per hundred cubic centimeters. The excretion of phenolsulfonphthalein was 60 per cent in 225 cc of urine within two hours. The results of electrocardiographic examination at this time were reported as follows: rate, 69, sinus bradycardia, preponderance of the right ventricle, an isoelectric T wave in lead III, a lengthened Q wave in lead III, a notched QRS complex in lead II and a slurred QRS complex in leads I and III. When the blood pressure was taken hourly over a twenty-four hour period the variations were: systolic, 115 to 150, and diastolic, 70 to 110 mm of mercury (fig 7).

In June 1933 the patient returned for reexamination. He was then 51 years of age. He was having some extrasystoles and an occasional tight feeling across the chest. His weight had decreased to 184 pounds (83.6 Kg). At a single determination the blood pressure was 150 systolic and 110 diastolic. The aortic second sound was accentuated, grade 2, but physical examination revealed no other changes. The patient's symptoms remained unchanged until December 1935, when for a period of several weeks he was under marked mental and physical strain. During this time he had several episodes of severe substernal distress. In some of these attacks there was definite projection of the distress to the left axilla and arm. Some alarm was felt concerning his condition, and he was placed in a hospital. He seemed to improve over a period of four weeks, but pleurisy suddenly developed on the right side, and he was confined to bed for another month. Numerous readings of the blood pressure during this period of hospitalization varied from 105 to 125 systolic and from 70 to 90 diastolic (table 2). Urinalyses showed only a trace of albumin and only an occasional cast. Determinations of certain constituents of the blood between December 25 and April 1 revealed a urea content of 43 mg, a creatinine content of 1.4 mg and a cholesterol content of 165 mg per hundred cubic centimeters. During this same period several examinations revealed a normal content of hemoglobin and a normal

number of erythrocytes On March 18 a roentgenogram of the thorax revealed a moderately enlarged cardiac shadow, apparently no greater than that seen in October 1931, four and a half years previously (fig 8)

Between Feb 27, 1931, and March 16, 1936, ten electrocardiographic tracings were taken Dr Barnes has reviewed these in detail, as in the previous case, and the following is a summary of his impressions "Right axis deviation was

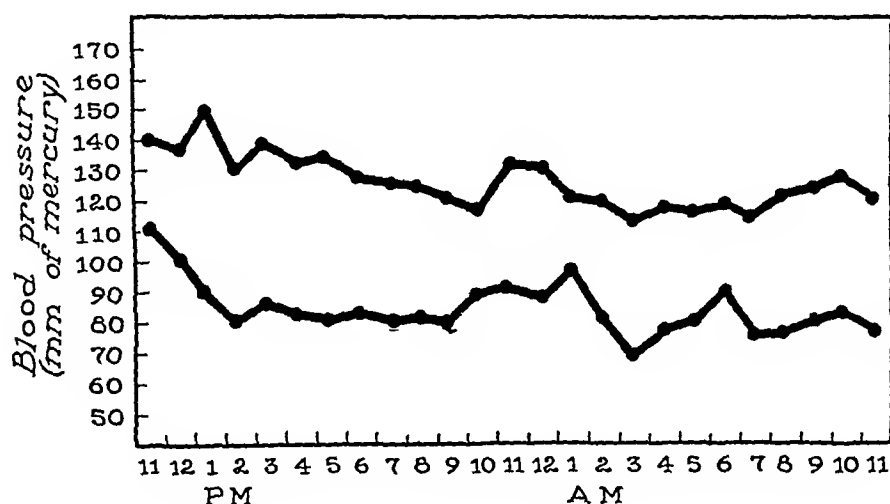


Fig 7 (case 2) —Blood pressure readings taken over a twenty-four hour period on Oct 7, 1931

TABLE 2—Blood Pressure Readings (Case 2)

Date	Blood Pressure, Mm Hg	
	Systolic	Diastolic
9/25/31	180	120
10/ 5/31	170	120
10/ 7/31*		
6/ 8/33	150	110
12/28/35	125	90
1/ 2/36	125	90
1/ 9/36†	105	70
1/11/36	110	70
1/22/36	115	85
2/10/36	105	70
2/13/36	120	80
2/16/36	120	80

* Variation in twenty four hour period systolic, 115 to 150, diastolic, 70 to 110

† Hemoglobin, 13.8 Gm per 100 cc, erythrocytes, 4,800,000 per cu mm leukocytes, 10,600 per cu mm

indicated in the first tracing (Feb 27, 1931) in spite of an expectancy of left axis deviation as a result of hypertension There was also an associated flattening or diphasic change in the T wave in lead I, however, when these changes were first observed there was no demonstrable increase in the width of the QRS complex Tracings taken from Dec 23, 1935, until March 16, 1936, revealed evidences of bundle branch disturbances, indicated by an increasing width of the QRS complex as well as notching or slurring or both A detailed study revealed that first the left and later the right bundle branches were involved At no time was the bundle branch defect complete, and in general it seemed of moderate degree

In view of the subsequent changes in the QRS complex it seems reasonable to assume that the bundle branch injury accounted for the earliest changes. All these changes may be interpreted as a result of sclerosis in the coronary arteries supplying the bundle branches. The tracings gave no evidence at any time of acute coronary occlusion."

In March the patient gradually became more active and resumed part-time work. The urine continued to be free from albumin and casts. Several ophthalmoscopic examinations were made subsequent to Oct 6, 1931, the last being made on April 20, 1936. There was always slight sclerosis of the retinal arterioles, but at no time was there any evidence of retinitis.

On April 6, 1936, the patient drove his car home from his office in the evening and as he alighted noticed numbness of the left foot. He thought that slight pressure on a nerve had resulted from his position while driving. This numbness increased, however, and after an hour he called a colleague, who discovered marked pallor of the leg and absence of pulsations from the vessels below the femoral



Fig 8 (case 2) —Teleroentgenogram of the thorax, March 18, 1936

artery. There was no pain. On April 8 the patient was found semiconscious, with complete left hemiplegia. From April 16 to 26 he had hiccups. His left foot then became gangrenous, and on May 2 amputation was performed through the mid-portion of the thigh. Histologic examination of a medium-sized artery from the amputated leg revealed marked destruction of the medial coat, with extensive deposits of calcium and atheromatous formation. There was thrombosis with beginning organization which completely occluded the lumen of the vessel (fig 9 A). There was ancient thrombosis of the accompanying vein, which was entirely organized and contained numerous canals.

On May 6 pulsations disappeared from the vessels of the right leg, and shortly after this it became evident that there was blockage of the circulation to the sacral, gluteal and lower lumbar regions. In this region a large infected decubital ulcer developed. The patient slowly became weaker and died on June 20.

Necropsy Observations—At necropsy the lining of the upper half of the aorta showed marked atherosclerosis, approximately 65 per cent of the lining being involved. Immediately below the origin of the renal arteries the aorta was com-

pletely occluded by a large organized thrombus which extended peripherally into both iliac arteries. There was a large antemortem thrombus in the lower portion of the inferior vena cava, approximately 12 cm in length.



Fig 9 (case 2) —*A*, an artery of the left leg, showing thrombosis and deposits of calcium in the arterial wall. Hematoxylin and eosin stain, $\times 30$. *B*, the abdominal aorta, showing atheromatous plaques containing cholesterol crystals. Hematoxylin and eosin stain, $\times 20$.

The heart weighed 525 Gm. There were moderate hypertrophy of the wall and dilatation of the chamber of the left ventricle. There was moderate to marked

atherosclerosis of the coronary arteries but no gross scarring of the myocardium. The kidneys together weighed 350 Gm. The capsules stripped easily, and they were architecturally well preserved. Also present were bronchopneumonia and purulent tracheobronchitis, with multiple infarcts in the spleen. The brain was not examined.

Microscopic examination of the aorta showed marked irregular narrowing and destruction, with fibrosis of the arterial wall. Large areas of the vessel showed atheromatous formation with cholesterol clefts. There was some deposition of calcium in the atheroma. Numerous areas of lymphocytes were scattered through the wall and in the adventitia. The picture was that of advanced atherosclerosis (fig 9B).

A section of the vena cava at the level of the thrombus showed almost complete occlusion, with numerous histiocytes and some blood pigment in the margin of the clot. The clot was adherent to the wall of the vein. The wall contained a moderate number of fibroblasts and a few lymphocytes. These findings indicated nonspecific thrombophlebitis, several weeks or even a few months old.

The cardiac muscle showed some variation in the size of the nuclei. One definite area of fibrosis was seen, but this was not extensive. There was some increase in the fibrous tissue between muscle fibers, and the small veins and venules appeared to be dilated. Arterioles appeared normal. These observations possibly indicated some chronic infarction and fibrosis of the myocardium, but there were insufficient sections to be certain of either.

In the liver some congestion was seen around the hepatic veins. Some fatty infiltration of the parenchyma was present, but the blood vessels were essentially normal. The lungs showed patchy bronchopneumonia and bronchitis of the small and terminal bronchioles. The pulmonary vessels were not abnormal.

COMMENT

Clinical Course—The complex nature of diffuse arterial and arteriolar disease is exemplified in these 2 cases. In case 1 the course was rapid, the hypertension sustained and the terminal phase explosive. The final clinical manifestations were due to marked dysfunction of the retina, choroid, central nervous system, heart and kidneys. We have noted previously a similar but more slowly developing terminal syndrome in so-called malignant hypertensive disease. A logical interpretation of such findings is that there is a simultaneous interference with the blood supply to these vital organs due either to acute vasospasm or to acute or chronic pathologic lesions in the majority of the arterioles. These and other facts indicate that there is a close relation between diffuse arteriolar dysfunction and hypertension. Of added interest in the first case was the history of initial fever and of fever during the last week of life together with polymorphonuclear leukocytosis. These clinical evidences of toxemia and the presence of inflammatory-like lesions in the small arteries suggest the possibility that the vascular disease was of infectious or toxic origin.

The relatively slower clinical course, the periods of comparatively good health and the mild hypertension in case 2 were associated with

the development of atherosclerotic lesions in the arteries. The terminal clinical picture was due to the development of thromboses in the vicinity of the atheromatous lesions. Strange as it may seem, actual coronary thrombosis did not occur. The moderate and fluctuating hypertension was probably due to a slight and nonprogressive disturbance of the arterioles.

Retinal Picture—The retinal change seen in case 1 was of the type which is usually spoken of as typical of "albuminuric retinitis", it was characterized by diffuse edema of the retina and of the optic nerve, with various hemorrhagic and exudative lesions and with visible changes in the retinal blood vessels. This retinitis is often considered to be primarily nephritic in origin. Of course, renal insufficiency may develop at the same time or soon after retinitis of this type, but the development of renal insufficiency may be delayed for a long period after the development of the retinitis. It is therefore improbable that the renal insufficiency in itself has any influence on the production of retinitis of this character. Retinitis rarely develops in these cases without the development coincidentally or previously of a considerable elevation of the blood pressure. A rapid elevation of blood pressure is usually accompanied by generalized and irregularly distributed localized narrowings in the arterioles of the retina. These arteriolar changes usually precede the retinitis. Since it is usually impossible to find histologic counterparts for these clinically visible irregularities in the arterioles, we like to consider this type of retinitis as angiospastic, especially since the changes in the vessels develop rapidly and may disappear rapidly and spontaneously.

In case 1 evidence of general and irregular narrowing of the arterioles in the retina was extreme, particularly in some of the smaller branches of the arterioles, and this narrowing developed rapidly, certainly within a few weeks. These retinal changes suggested that there was a rapidly developing lesion of the small arterioles throughout the body. In addition to the usual lesions of angiospastic retinitis, subretinal edema was present in amounts sufficient to detach the retinas measurably. The source of this edema was probably the vascular lesions in the choroid which we originally interpreted, possibly incorrectly, as being angiospastic. In any event, the presence of these lesions suggested that the vascular disease was even more widespread and that it involved larger vessels than are affected in the usual case of vasospastic hypertension. This widespread distribution and unusual nature of the lesions in the small arteries and arterioles were demonstrated at necropsy.

In contrast with the observations in case 1, the retinal changes in case 2 were minimal. They consisted of mild arteriovenous compression

and mild narrowing of the retinal arterioles, also present was a slight change in the color of the arterioles. These ophthalmoscopic signs are interpreted by some to represent an increase of vasomotor tone in the arterioles, but we like to think of them as indicating a mild thickening of the media residual to a mild angiospastic episode, similar in type but less severe in degree than that seen in acute vasospastic hypertension. In cases of this type in which the angiospastic episodes do not recur, these retinal changes will remain constant for years, as they did in this particular case. Examination of the retina in this case during the last few months of the patient's life still showed mild sclerosis of the retinal arterioles, in spite of the fact that the blood pressure had returned practically to normal. In patients with mild hypertension and marked sclerosis of the larger arteries, the changes in the choroid arteries are more marked than those in the retinal arterioles. Sclerosis of the choroid arteries occurs quite regularly with increasing age, and it can often be demonstrated histologically when it has not been noted clinically. When sclerosis of the choroid vessels develops prematurely, between the ages of 45 and 60 years, it is usually associated with atherosclerosis of the larger vessels of the body and often with coronary sclerosis. In this particular case we are not able to say whether there was a definite histologic thickening of the choroid arteries because the eye was not available for histologic study.

*Pathologic Changes*³—In 1928 Kernohan and two of us (Dis Keith and Wegener)⁴ reviewed a series of cases of so-called malignant hypertension. The fact was stressed that in these cases the diffuse arterial disease not only involved the vessels of the kidneys but affected many of the arteries and arterioles throughout the body. Since then we have applied the term diffuse arterial disease to similar conditions, but we realize that it is a broad term and should include unique examples, such as in the present cases. In case 1 the diffuse vascular process had distinctive features which were different from those in so-called malignant hypertension and also from those observed in case 2.

At necropsy in case 1 the most significant gross finding was the presence of visible multiple infarcts on the surface of the kidneys. These infarcts produced a condition essentially that of symmetric cortical necrosis, the type of necrosis usually present in cases of severe eclamptic toxemia.⁵ The development of these infarcts readily explained

3 Dr J W Kernohan assisted in interpreting the pathologic changes in these cases

4 Keith, N M, Wegener, H P, and Kernohan, J W. The Syndrome of Malignant Hypertension, *Arch Int Med* **41** 141-188 (Feb) 1928

5 Evans, N, and Gilbert, E W. Symmetrical Cortical Necrosis of the Kidneys. A Report of a Case, *Am J Path* **12** 553-560 (July) 1936

the sudden appearance of large numbers of erythrocytes in the urine and the subsequent rapid failure of renal function. It was also significant that detachment of the retina and hemorrhages within its structure could be seen with the naked eye. On histologic examination there were few if any pathologic alterations in the retinal arterioles, but there were marked changes in some of the choroid arteries. These microscopic observations corroborated the previous ophthalmoscopic findings. The presence of small scattered areas of chronic tuberculosis did not seem significant etiologically with regard to either the vascular lesions or the presence of hypertension. On the contrary, it has long been claimed that chronic pulmonary tuberculosis is accompanied by hypotension. Mention should also be made of the absence of histologic changes in the retinal and intracerebral arteries and arterioles. Such negative evidence of organic disease strengthens the supposition that angiospasm is an important factor in causing the serious retinal and cerebral symptoms.

Ten years ago Kernohan, Anderson and one of us (Dr Keith)⁶ began to measure the diameter of the arterioles in diffuse arterial disease, as no previous systematic attempt had been made to ascertain the normal ratio between the thickness of the wall and the diameter of the lumen. They found the normal ratio in the arterioles of voluntary muscle to be approximately 1:2, and in many cases of serious arterial disease the ratio was reduced even to 1:1. The arterioles in the pectoral muscle in case 1 showed marked thickening, chiefly of the media, and the ratio of the thickness of the wall and the diameter of the lumen was about 1:1. We have considered this hypertrophy of muscle as being secondary to strain and possibly to the hypertension. Many arterioles of various organs throughout the body showed a similar lesion. However, the smaller arteries in many organs revealed other types of pathologic change. In a small artery of the pancreas the intima was greatly thickened, the intimal cells being "piled up" and the media almost destroyed. On the other hand, a small artery in the heart revealed almost complete obliteration, with periarteritis around it and enlargement of many of the nuclei within its wall. The occurrence of this periarteritis, an inflammatory-like change, in many widely distributed small arteries in case 1 and in arteries of corresponding size in the kidneys in 2 cases of severe hypertension reported by Klemperer and Otani⁷ suggested a similarity to the lesion in periarteritis nodosa.⁸

6 Kernohan, J. W., Anderson, E. W., and Keith, N. M. The Arterioles in Cases of Hypertension, *Arch. Int. Med.* **44**: 395-423 (Sept.) 1929.

7 Klemperer, P., and Otani, S. "Malignant Nephrosclerosis" (Fahr), *Arch. Path.* **11**: 60-117 (Jan.) 1931.

8 Kernohan, J. W., and Woltman, H. W. Periarteritis Nodosa, *Arch. Neurol. & Psychiat.* **39**: 655-686 (April) 1938.

These lesions in our case 1 would possibly explain the presence of fever and leukocytosis and also the severe pains in the legs and arms. There is still, however, much mystery regarding the primary cause of periarteritis nodosa.

The hyalin-like necrosis of the media of some of the choroid arteries was regarded by Dr Kernohan as representing the earliest phase in the development of the lesions of periarteritis nodosa. It is of interest in the case of periarteritis nodosa with "albuminuric retinitis" described by Friedenwald and Rones⁹ that the periarterial lesions were present in the choroid but not in the retina and that they were in a well developed, almost terminal stage. Friedenwald said he considered that the retinitis was due to the arteriolosclerotic lesions in the retina, which were identical with those seen in the usual case not associated with periarteritis nodosa. In our case 1, death occurred too rapidly for arteriolosclerosis to develop in the retina, but we feel justified in attributing the retinitis proper to the spastic constriction of the retinal arterioles rather than to the early inflammatory lesions in the vessels of the choroid.

It is much easier to explain the pathologic picture in case 2 than that in case 1. The fundamental change in case 2 was that of arteriosclerosis, and histologic sections of the abdominal aorta showed all the typical features of this condition, including calcified areas, ulceration and cholesterol crystals.

At this juncture several facts regarding arteriosclerosis are worthy of consideration. First is the question of age. One naturally expects to encounter arteriosclerosis in elderly persons. It may, however, begin in children and gradually progress through life. In some instances the disease progresses slowly, but in others it begins early and progresses relatively rapidly and leads to the results seen in our case 2. Heredity probably plays a role in the occurrence of arteriosclerosis, but exact data for the proof of such an assumption are lacking. Aschoff¹⁰ claimed that atheromatous deposits in the arteries are frequently associated with, and possibly secondary to, a high cholesterol content of the blood. In our case 2 the cholesterol concentration of the plasma was within the normal range, so that hypercholesteremia is not always demonstrable. This is in agreement with the findings of Duff.¹¹ Finally, there is little direct evidence of an exact relation between arteriosclerosis and hypertension.

9 Friedenwald, J. S., and Rones, B. Some Ocular Lesions in Septicemia, *Tr. Am. Ophth. Soc.* **28**: 286-300, 1930.

10 Aschoff, L. *Lectures on Pathology*, New York, Paul B. Hoeber, 1924.

11 Duff, G. L. Experimental Cholesterol Arteriosclerosis and Its Relation to Human Arteriosclerosis, *Arch. Path.* **20**: 81-123 (July), 259-304 (Aug.) 1935.

CONCLUSIONS

The term diffuse arterial disease when used in a broad sense includes cases in which there are primary changes both in the arteries and in the arterioles. Two contrasting cases are reported in which the preponderant alteration in 1 was in the arterioles, whereas in the other it was in the arteries. The general conclusion is drawn that in patients with sustained hypertension, the site of the predominating change, whether it is an abnormal physiologic process or an actual anatomic lesion, is in the arterioles, on the other hand, in patients with diffuse atherosclerosis of the arteries, hypertension is often mild and fluctuating or even absent.

Progress in Internal Medicine

VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE, WITH A CRITICAL
REVIEW OF THE SURGICAL TREATMENT

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A REVIEW OF SOME OF THE RECENT LITERATURE

BY DR SCUPHAM AND DR VAN DELLEN

In the past year the importance of general involvement in the course of vascular diseases has been emphasized by a number of writers. In association with this idea, primary vascular hypertension has been occupying a much larger place in investigative interest. For this reason a brief résumé of some of the work on this subject will be included in this review.

No attempt will be made to discuss all the papers which have been published, but certain ones have been selected which seem to be contributions to the knowledge of vascular diseases. In some instances material has been included which has been covered, at least in part, in previous reviews. This has been done because the subject seems to bear the emphasis of repetition without becoming commonplace.

PHYSIOLOGY

In the annual George E Brown lecture, Cannon¹ reviews the factors affecting vascular tone. The term is used to designate a state of moderate contraction of the elements in the walls of the blood vessels. This state may be decreased or increased by the operation of various factors. In discussing the effect of sympathectomy he quotes the evidence which indicates that vascular tone returns to an approximate normal level after

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1 Cannon, W B Factors Affecting Vascular Tone, *Am Heart J* **14** 383, 1937

sympathectomy in animals After local section of the vasoconstrictor nerves the blood vessels regain their normal tone in a variable length of time Cannon states that the evidence is clear on this point After complete denervation of the sympathetic nerves there is eventually a return of the blood pressure to approximately the normal level after a short interval The restoration of the blood pressure level after sympathectomy may be partly due to an increase in the volume of blood The effect of section of the sympathetic nerves on smooth muscle, rendering it more sensitive to epinephrine, is considered in detail in Cannon's discussion That this effect is not due solely to the effect of epinephrine is pointed out The substance sympathin must be considered It is discharged into the blood stream under the same conditions as is epinephrine, that is, with emotional excitement, hypoglycemia, cold, pain and vigorous muscular activity It is probable that both sympathin and epinephrine collaborate in producing this effect Whether or not there is another gland of internal secretion which supplies the chemical agent that might act for the restoration of tone in sympathectomized vessels is not known It is likewise not certain that any hormonal substance is necessary for the restoration of tone Cannon believes that this may be regarded as an intrinsic property of smooth muscle itself The variations in blood flow which have been observed after the application of heat to denervated vessels may be determined by the metabolic needs of the tissues or may be the consequence of the change of temperature in the vessels themselves

That smooth muscle may be relaxed by nerve stimulation has long been known In the completely sympathectomized animal there is a fall in blood pressure after vigorous muscular activity This has been explained as an effect of muscular metabolites on the vessels, producing vasodilatation Cannon states that this occurs too rapidly to be explained on this basis There is evidence which supports the view that there is actually a vasodilator center in the floor of the fourth ventricle It is probable that the route by which impulses reach the periphery after a stimulus in completely sympathectomized animals is through the dorsal roots

There are three explanations for the production of excessive tone such as that which occurs in hypertensive states One is the excessive discharge of vasoconstrictor impulses from the central nervous system An abnormal narrowing of the vascular channels might be produced in such a manner Evidence for this is the hypertension which develops after all the restraining nerves are severed These are the cardioaortic and carotid sinus plexuses The second condition is that blood vessels, even though normally innervated, may become especially sensitive to natural stimuli, much in the manner of the paroxysm in Raynaud's disease The third way in which general vasoconstriction might develop

is through peripheral stimulation of the smooth muscle by unusual chemical agents. This is still an unknown factor.

Blood Cholesterol—The relation of lipid metabolism to vascular diseases has been discussed in previous reviews. Alterations in the cholesterol content of the blood have been reported by various observers.

Jacobi,² in treating diseases of this type with intravenous injections of solutions, noted rather marked changes in the cholesterol values of the blood. He and his associates employed solutions of 2 per cent sodium iodide in physiologic solution of sodium chloride or 2 per cent solution of sodium chloride. Most of the patients whom they treated had painful ulcerative lesions of the extremities. During the course of treatment the only significant changes noted in chemical studies of the blood were in the cholesterol levels. Before treatment these values were either subnormal or in the low normal range. After the use of chloride or iodide solutions for a short time a sharp rise in the cholesterol value was invariably noted. This was followed by a subsequent fall to the normal level as treatment was continued. In some instances the height of the cholesterol response amounted to almost three times the initial figure. It was also noted that the lower the initial cholesterol value, the more marked the relief from pain and the more rapid the healing process after the introduction of this type of treatment. For those patients in whom the disease recurred after treatment, the cholesterol level was again found to be lowered. This decrease was found to occur before the return of pain or ulceration. The mechanism of this response is still uncertain, and further observations should be made to throw light on what may be an important feature of obstructive vascular disease.

Plethysmographic Studies—Several types of plethysmographs have been used for the study of circulation. Turner³ has devised an instrument of this type for the measurement of the changes in volume due to pulsation in a portion of the finger. The apparatus makes a graphic record of pulse volumes as small as 0.1 cu. mm. and of gradual changes in volume as great as 1,000 cu. mm. A series of studies with this device have been reported.

Sodeman⁴ describes a method for estimating the volume of soft tissues in the portion of the finger used with this instrument. This

2 Jacobi, H. G. The Blood-Cholesterol Response to Intravenous Therapy in Peripheral Arterial Disease, *Am J M Sc* **193** 737, 1937.

3 Turner, R. H. Studies in the Physiology of Blood Vessels in Man, Apparatus and Methods. I. A Sensitive Plethysmograph for a Portion of the Finger, *J Clin Investigation* **16** 777, 1937.

4 Sodeman, W. A. Studies in the Physiology of Blood Vessels in Man, Apparatus and Methods. II. A Method for the Determination of the Volume of the Soft Tissue About the Terminal Phalanx of the Human Finger, *J Clin Investigation* **16** 787, 1937.

consists of measuring the total volume, estimating the volume of bone and subtracting the latter from the former. With this apparatus Turner, Burch and Sodeman⁵ have made some observations on the effects of raising and lowering the arm on the pulse volume and blood volume of the finger tip in normal persons and in a few patients with vascular diseases. A change in pulse volume was found in all instances with a change in the level of the hand. The pulse volume increased with the elevated position and decreased with the lowered position, while the blood volume of the finger tip varied in the opposite way in most instances. In subjects with arteriosclerosis only, the mean volume of pulsation was approximately the same as that in normal subjects, while the mean total blood volume of the finger part was less. In instances of diastolic hypertension the volume of pulsations and the total blood volume were measured with the hand at the level of the heart, and it was found that with an elevated position these values were reduced. The total blood volume was essentially normal, but the pulsation volume was diminished. With the hand 45 cm below the level of the heart the total blood volume was reduced, but the volume of pulsation was similar to that for the normal group. In 1 subject with a localized Raynaud phenomenon with atrophic changes in the left index finger, distinct changes were noted in comparison with the corresponding normal finger of the other hand. The involved finger showed a reduced total volume of blood in all positions that was out of proportion to the reduction in the total volume of soft tissues. The volume of pulsations was slightly reduced at the cardiac level and definitely so in both the elevated and the lowered position. The changes in all instances, they believe, are due to actual change in the relation of the volume of blood to the volume of soft tissues. The pulse wave is manifested by changes in volume in those vessels which contribute most to the color of the skin, and these vessels are dilated in the depressed and narrowed in the elevated position. These vessels are the capillaries and venules. The increase in the total volume of blood in the fingers in the depressed position and its diminution in the elevated position, they believe, are due to changes in the caliber of the veins and occur in spite of changes in the opposite direction in the arterial vessels. They state that in normal subjects there seems to be no significant correlation between pulse pressure and pulse volume. The influence of position on pulse volume they ascribe to changes in the distensibility of both

5 Turner, R. H., Burch, G. E., and Sodeman, W. A. Studies in the Physiology of the Blood Vessels in Man. III. Some Effects of Raising and Lowering the Arm upon the Pulse Volume and Blood Volume of the Human Finger Tip in Health and in Certain Diseases of the Blood Vessels, *J. Clin. Investigation* 16: 789, 1937.

arterial and venous vessels and to changes in smoothing effect on the pulse wave. The same authors studied the changes in volume following sudden occlusion. They observed not only primary swelling of the finger following sudden occlusion but also a spontaneous secondary diminution in volume. This occurred only when pressures between 40 and 50 mm of mercury were employed for occlusion. If pressures above this level were used, only swelling occurred. They believe these reactions are due to the distention of the small veins and capillaries and the subsequent loss in volume due to active constriction of these vessels. This is probably initiated as a response to the increased tension in these vessels.

Heitzman⁶ reports an interesting method for estimating the amount of blood in the fingers and toes by means of a photoelectric cell. This device is attached to the string galvanometer of an electrocardiograph, and variations in the volume of blood in the part are recorded by the camera of the instrument. The form of the records produced conforms, in general, to the transmission type of plethysmograph and lends itself well to clinical use in the dynamic analysis of the peripheral circulation. Apparently this method may be used to study the effects of various procedures on digital pulse volume as well as the form and amplitude of the pulse volume of the fingers or toes. In a comparison of the effect of amyl nitrite on pulse volume the results were similar to those obtained with an optically recording plethysmograph. This interesting method of studying the peripheral blood vessels has been applied by the author to the nasal septum and apparently may be used in many other portions of the body. The method seems valuable and certainly should be useful in studying qualitative changes.

Ratschow⁷ describes a simple ergometer with which, he believes, considerable information may be obtained. This apparatus not only will aid in determining the efficiency of the arterial supply to the muscles in cases of early vascular disease but will serve to differentiate other forms of pain in the extremities which may be easily confused with the pain of vascular impairment. It is likewise a method by which information can be gained entirely on an objective basis as to the progress and effect of therapy. He points out that while rest is essential in the treatment of such disorders in cases in which the condition is progressing to healing, limited exercise may be given if this apparatus is used. The apparatus can be quantitatively adjusted so that no harm

6 Hertzman, A. B. Photoelectric Plethysmography of the Nasal Septum in Man, *Proc Soc Exper Biol & Med* **37** 290, 1937, Photoelectric Plethysmography of the Fingers and Toes in Man, *ibid* **37** 529, 1937.

7 Ratschow, M. Der Arbeitsversuch, eine einfache Methode zur Erkennung und Berteilung peripherer arterieller Durchblutungsstorungen, *Munchen med Wchnschr* **84** 1128, 1937.

will be done if the amount of exercise is restricted to a point less than that which will produce pain or discoloration of the extremity

Intra-Arterial Injection of Drugs—Allen and Crisler⁸ studied the effect of the intra-arterial injection of papaverine hydrochloride, acetyl-beta-methylcholine chloride and histamine phosphate on the peripheral cutaneous temperature. The temperature of the fingers in all instances rose to a much higher degree than did that of the toes. This occurred regardless of the location of the injection, whether given in the femoral or in the brachial artery or whether given intramuscularly or intravenously, when papaverine was given. It was found impossible to fix a drug of this type in any extremity. The lower extremities seem to be relatively refractory to such vasodilating drugs. They believe that the refractoriness of vasodilatation of the lower extremities is intimately associated in some, as yet unexplained, way with the much higher incidence of chronic occlusive arterial diseases in the lower extremities as contrasted to their incidence in the upper extremities.

In studying the effect of epinephrine on the digital arterioles of man, Fatherree and Allen⁹ found that the demonstration of the vasoconstrictor effect on the digital arterioles was dependent on the presence of sufficient vasodilatation preceding the experiment. Even when vasodilatation was present, the injection of epinephrine hydrochloride intravenously, according to the method of Freeman, Smithwick and White, did not always cause significant vasoconstriction in persons with normally innervated extremities. The vasoconstrictor effect of this drug varies widely in different persons. There was even marked variability of response in the same individual at the same temperature. So much variation was encountered that the response of the temperature of the skin did not seem to be a reliable estimate of the effect of the drug. According to the writers, patients with vasomotor symptoms suggesting Raynaud's disease do not have arterioles which are unduly sensitive to epinephrine. Those persons in whom the reaction demonstrated that the arterioles were more than usually sensitive had no evidence of vasomotor disease. The authors do not believe that the recurrence of vasomotor symptoms after ganglionectomy for Raynaud's disease can be due to increased sensitivity of the arterioles to epinephrine.

On the basis of the effect of sodium nitrite on the peripheral vascular bed,¹⁰ this drug has been employed in testing the flexibility and integrity

8 Allen, E. V., and Crisler, G. R. The Result of Intra-Arterial Injection of Vasodilating Drugs on the Circulation. Observations on Vasomotor Gradient, *J. Clin. Investigation* **16** 649, 1937.

9 Fatherree, T. J., and Allen, E. V. The Influence of Epinephrine on the Digital Arterioles of Man. A Study of the Vasoconstrictor Effects, *J. Clin. Investigation* **17** 109, 1938.

10 Beck, W. C., and de Takats, G. The Use of Sodium Nitrite for Testing the Flexibility of the Peripheral Vascular Bed, *Am. Heart J.* **15** 158, 1938.

of the peripheral arteries, 0.04 Gm of freshly dissolved sodium nitrite in water being injected intravenously. Before the injection is made an oscillometric curve is obtained. The effect of the drug becomes apparent in ten or fifteen minutes, after which time a second oscillometric curve is obtained for comparison with the original. No significant fall in blood pressure occurs with the amount of the drug used. The writers believe that the drug acts primarily on the terminal arteries with a secondary arteriolar constriction in order to maintain the blood pressure. Even patients with marked hypertension show no significant fall in blood pressure. The capacity for maximum vasodilatation depends chiefly on the amount of organic damage present.

Killian and Oclassen¹¹ made some observations on the relative effects of water baths and mustard baths at varying temperatures on the rate of peripheral blood flow. Observations were made by means of a plethysmograph. Water baths at 38 and 40 C had a definite effect in increasing the blood flow in both the hands and the feet. When 6 per cent of mustard was added, the rate of blood flow increased as much as 74 per cent above that when water alone was used at these temperatures. Cooling the surface of the skin reduced the rate of blood flow. At temperatures of 25 to 30 C, mustard baths did not affect the rate of blood flow in the foot more than did the water bath at the same temperature. At temperatures between 35 and 40 C the mustard bath did increase the rate of blood flow from 17 to 69 per cent above the average rates of flow in water baths at these temperatures. Above 40 C there was relatively little difference whether mustard was added to water or not.

Capillaries—Bordley, Grow and Sherman¹² report some interesting observations on the capillaries of the skin of the leg. These observations indicate that the flow of corpuscles through individual capillaries of the human skin is controlled by a mechanism residing in the capillaries themselves under normal conditions. The circulation through individual capillaries is frequently intermittent, in fact, intermission in flow may occur alternatively in capillaries arising from the same arteriole. When the flow ceases in a capillary, the vessel may become completely empty of corpuscles. These findings indicate confirmation of the views previously reported that capillaries have an individual function in regulating the flow of blood through them.

11 Killian, J. A., and Oclassen, C. A. Comparative Effects of Water Baths and Mustard Baths at Varying Temperatures on the Rate of Peripheral Blood Flow in Man, *Am Heart J* **15** 425, 1938.

12 Bordley, J., III, Grow, M. H., and Sherman, W. B. Intermittent Blood Flow in the Capillaries of Human Skin, *Bull Johns Hopkins Hosp* **62** 1, 1938.

Springorum¹³ emphasizes the importance of the blood vessels of the skin as far as their effect on the circulatory system is concerned. This relation is particularly important in regard to the injection of vasodilator drugs when the shift of blood to these vessels may be great enough to bring about collapse. Important variations may occur in association with changes in temperature, so that under certain conditions even changes in arterial blood pressure may result.

Temperature of the Skin—Sheard, Williams and Horton¹⁴ have studied the role of the extremities in the exchange of energy between the normal human body and its environment. They conducted experiments under controlled conditions and recorded the temperature of the skin in various locations. They found that the surfaces of the head and trunk play only a small part in the regulation of body temperature, that is, in the maintenance of the balance between internal heat production and heat elimination. The upper portions of the arms and legs maintain a fairly uniform range of temperature, from 30 to 35 C. The lower portions of the extremities play the main role in regulating body temperature through a much greater shift of blood and an increased flow to the skin. When the body is exposed to room temperatures at 60 to 65 F the temperature of the fingers and toes tends to approach that of room temperature. As the room temperature is raised the amount of heat dissipated is increased. At higher environmental temperatures the temperature of the fingers approaches that of the head and trunk. With increased internal heat production the extremities show a rise in temperature and play an important part in heat elimination. Persons with peripheral vascular disease do not show the same heat control pattern that normal persons show.

Friedlander, Silbert, Bierman and Laskey¹⁵ have made some interesting observations on the relation between the temperature of the skin and the temperature of the muscles of the lower extremities under certain conditions. The application of heat to the upper extremities, according to the method of Landis, produced striking elevation in the temperature of the skin of the feet, but the temperature of the muscles of the legs remained unchanged. Similar observations were made after the paravertebral injection of procaine hydrochloride. Spinal anesthesia was followed by marked elevation of the temperature of the skin, while

13 Springorum, P. W. Die Bedeutung der Hautgefasse fur den Gesamtkreislauf, *Klin. Wchnschr.* **17** 11, 1938.

14 Sheard, C., Williams, M. M. D., and Horton, B. T. The Exchange of Energy Between the Normal Human Body and Its Environment. I. The Role of the Extremities, *Proc. Staff Meet., Mayo Clin.* **13** 13, 1938.

15 Friedlander, M., Silbert, S., Bierman, W., and Laskey, N. Differences in Temperature of Skin and Muscles of the Lower Extremities Following Various Procedures, *Proc. Soc. Exper. Biol. & Med.* **38** 150, 1938.

the temperature of the muscles remained unchanged. Intravenous injection of hypertonic solutions of sodium chloride was followed by elevation of the temperature of both skin and muscles. Intramuscular injections of extract of pancreatic tissue were not followed by any change in the temperature of the skin or muscles. Intravenous injections of epinephrine hydrochloride produced a striking rise in the temperature of muscles which had a good circulation and produced a fall in the temperature of the skin when the circulation was impaired. The increase in the temperature of the muscles was less marked. They point out that the usual assumption that an increase in the temperature of the skin is an indication of increased circulation is apparently not true as far as the blood supply to the muscles is concerned. The failure of various methods of increasing the temperature of the skin to relieve intermittent claudication is explained by these conditions.

Collateral Circulation—Some interesting experiments have been reported by Stein¹⁶ on the development of collateral circulation in the ear of the rabbit after ligation of the main arteries. An extensive collateral circulation developed within a few days. Instead of the normal regular, definite pattern, that of the collateral circulation was irregular and aimless. The vessels were increased in number, they were tortuous and varied widely in size. The circulation was adequate to meet the needs of the tissue, and most of the vascular reactions were normal except when ligation was made low.

Under controlled conditions these ears were subjected to treatment with positive and negative pressure. In the ears so treated vascular spasms occurred, and cyanosis became marked. Anoxemia developed which finally resulted in necrosis.

In an arteriographic study of the vessels in the lower extremities of patients who had suffered occlusion of large arteries, Yater¹⁷ was able to visualize the method by which the collateral circulation developed. The occluded portions of the vessels were seen to be bridged across by long, fine, irregular branches so that the lumen of each vessel above the point of occlusion was connected with that below. The function of the main artery was thus reestablished. The number, character and size of the collateral channels seemed to vary considerably. Most collateral vessels seemed to be enlarged and elongated branches that existed before the onset of vascular disease. New anastomoses probably developed, since, as the author indicates, it is unlikely that a branch of an

16 Stein, I. D. Studies of the Collateral Circulation Following Experimental Vascular Occlusion, *Am Heart J* **14** 726, 1937.

17 Yater, W. M. Maintenance of the Functional Integrity of Occluded Large Arteries as Demonstrated by Thorotrast Arteriography, *Am J M Sc* **194** 372, 1937.

artery normally empties into the same vessel a short distance below its origin

These observations are in essential agreement with those previously reported. They demonstrate again the value of arteriography in the study of the mechanism of the circulation in abnormal states and in individual instances in the decision on the prognosis and subsequent program of treatment.

Effects of Tobacco—While tobacco smoking cannot be regarded as an etiologic factor in any of the diseases of the vascular system, there seems to be a definite tendency to believe that it plays an important part in vascular diseases of all types.

Chapman¹⁸ has reviewed the experimental and known effects of tobacco on the vascular system. He states that there is sufficient information to prove that tobacco is definitely harmful to those who possess a vascular system which is unduly subject to vasoconstriction. This is true not only in thromboangitis obliterans but in arteriosclerotic diseases as well.

The average percentages of nicotine range as follows: in pipe tobacco, from 1.45 to 2.84 per cent; in cigars, from 0.91 to 1.8 per cent; and in cigarettes, from 1.06 to 3.11 per cent. Nicotine is considered the most important deleterious factor in tobacco. The absorption in the mouth during smoking is estimated to be 66 per cent, and if the smoke is inhaled, as much as 88 per cent of the nicotine is absorbed. There is no difference in the effect on the vascular system even though so-called denicotinized tobacco is used. The amounts of nicotine and of irritating by-products in tobacco are increased by the amount of moisture in the tobacco, the rapidity of smoking and the tightness of packing. The last third of a cigar or cigaret will produce 15 per cent more nicotine in the smoke than the first portions.

Minnhaar¹⁹ has studied the effects of tobacco smoking experimentally and has carefully observed its clinical effects. His findings are in accord with those of previous observers. He states that the effect of smoking in cardiovascular disease varies with the constitution of the patient and with the local reaction of the arteries of the heart and of the lower extremities. He concludes that smoking has a definite harmful action on the cardiovascular apparatus.

Golston²⁰ emphasizes the functional effect on the arteries of the heart and of the peripheral circulation. He states that the continued

18 Chapman, D. G. The Effects of Tobacco Smoking on the Vascular System, *Virginia M. Monthly* **64** 454, 1937.

19 Minnhaar, T. C. Pathogenic Role of Tobacco Smoke in Cardiovascular Disease, *Rev. med. del Rosario* **27** 706, 1937.

20 Golston, H. The Tobacco Heart, *Virginia M. Monthly* **64** 319, 1937.

use of tobacco may cause the development of organic disease and that the vasoconstriction which results may be a contributing cause of death or impairment of tissue integrity

Herrell²¹ reports an interesting case in which there was marked idiosyncrasy to tobacco. This patient showed the usual effects of cigaret smoking on the vascular system to a marked degree. In fact, the vascular reactions were so pronounced that severe subjective symptoms resulted. The demonstrable effects were an acceleration of cardiac rate, a sharp rise in blood pressure and a lowering of the temperature of the skin to an unusual degree. Cutaneous tests for sensitiveness to tobacco were performed with negative results.

Nye,²² who has made some observations on the frequency of vascular diseases among Australian aborigines, found few instances of disease of this type. He states that these natives smoke a great deal and use the strongest kind of trade tobacco. It is his opinion that tobacco plays only a small part in the development of arteriosclerosis or hypertension.

Thienes and Butt²³ have been of the opinion that much of the work incriminating tobacco and nicotine as causing degenerative vascular disease in experimental animals is highly uncritical and based on poorly controlled experiments. In the repetition of some of this work they were impressed with the degenerative changes they found in their control animals, which often showed more evidence of vascular disease than those exposed to chronic nicotine poisoning. They conclude only that the acute peripheral vasoconstriction associated with the smoking of tobacco may exaggerate the effect of degenerative vascular disease of the extremities.

THROMBOANGIITIS OBLITERANS

Goodman²⁴ has made further studies on the relation of typhus fever to thromboangitis obliterans. In considering the etiology of this disease he believes that all the factors except infection have been eliminated. Studies of the epidemiology of typhus fever indicate that there is an unusual coincidence of the two conditions. These diseases have occurred in large numbers of persons in the same classes, and typhus fever is

21 Herrell, W. E. Idiosyncrasy to Tobacco, *Proc. Staff Meet., Mayo Clin.* **13** 1, 1938.

22 Nye, L. J. Blood Pressure in the Australian Aboriginal with a Consideration of Possible Aetiological Factors in Hypertension and Its Relation to Civilization, *M. J. Australia* **2** 1000, 1937.

23 Thienes, C. H., and Butt, E. M. Chronic Circulatory Effects of Tobacco and Nicotine, *Am. J. M. Sc.* **195** 522, 1938.

24 Goodman, C. Thrombo-Angitis Obliterans and Typhus. Evidence of Etiologic Relationship, *Arch. Surg.* **35** 1126 (Dec.) 1937.

disseminated in its endemic form throughout the world. He points out that typhus is primarily a disease of the blood stream, the organisms eventually becoming embedded in the endothelial cells of the blood vessels. There is a proliferative reaction of the endothelium followed by thrombosis and complete occlusion in some instances. Gangrene is commonly a complication of typhus, and many patients show symptoms similar to those of thromboangitis obliterans, according to the writer. The basis of the similarity is in the epidemiologic and pathologic pictures of these two diseases, which he noted as early as 1916. He undertook cutaneous tests with a vaccine prepared from the rickettsial organisms in both conditions. These tests were carried out with controls. The vaccine gave uniformly positive reactions in persons who had thromboangitis obliterans or Brill's disease or who gave a history of typhus fever. The same tests employed on persons with gangrene from other causes, such as arteriosclerosis and diabetes, gave entirely negative reactions. These observations deserve further study.

Costantini, Liaras and Bougeon,²⁵ in discussing the gangrene associated with typhus fever, state that they do not find the same similarity described by Goodman but that the gangrene of typhus is usually of the dry type, involving either an extensive portion of the skin or a portion of the extremities. It usually occurs in the lower extremity. Then the skin alone is involved, usually a dry black plaque is formed with clear-cut borders. The plaque is cast off, and the resulting wound is rapidly recovered with skin. The nodule of Franckel is the specific lesion. The site of predilection is along the vessels. If such a lesion causes obstruction to the flow of blood, tissue impairment will follow.

Weber²⁶ comments on the relative infrequency of familial cases of thromboangitis obliterans as reported in the literature and describes typical examples of the disease in a father and son.

Several reports of the occurrence of cerebral involvement in the course of thromboangitis obliterans have come to attention. Giampalmo²⁷ discusses this localization of the disease. Meszaros,²⁸ Uyama²⁹

25 Costantini, M, Liaras, and Bourgeon. Remarques sur les gangrenes du typhus exanthematique, *Presse med* **46** 75, 1938.

26 Weber, F. P. Thrombo-Angitis Obliterans in Father and Son, *Lancet* **2** 72, 1937.

27 Giampalmo, A. Beitrag zur Endarteritis obliterans des Gehirns, *Deutsche Ztschr f Nervenhe* **144** 166, 1937.

28 Meszaros, K. Thrombo-Angitis obliterans mit Veränderungen am Augenhintergrund, *Deutsches Arch f klin Med* **180** 526, 1937.

29 Uyama, Y. Ueber das Vorkommen der sogenannten "Thrombo-Angitis obliterans am Auge" unter Berücksichtigung anatomischer Untersuchungen *Arch f Ophth* **137** 438, 1937.

and others ³⁰ describe cases in which there were alterations in the vessels of the brain and fundi. Hausner and Allen,³¹ in a review of 500 cases, found clinical evidence of cerebral involvement in 3 per cent. They comment on the rapid disappearance and recurrence of the neurologic manifestation noted in several cases. Psychic symptoms, such as confusion and irrational behavior, occurred with the onset of hemiplegia. In 3 cases hemiplegia preceded the symptoms of involvement of the peripheral arteries by several years. They also state that a common complication is hemianopia. Anatomic studies were not made in any of these cases, but the symptoms occurred in cases which were typical examples of the disease and there was no other apparent etiologic factor. Reports of other types of visceral involvement have been made. They correspond with the reports of such cases made in previous years.

Tartakoff and Hazard ³² report a case in which there was a small growth in the spermatic cord, after surgical removal it showed the typical pathologic characteristics of thromboangitis obliterans. There was no other localization of the disease.

Littauer and Wright ³³ report an unusual case in which there were acute ulcerations on all four extremities which occurred simultaneously.

ARTERITIS

In a paper in which he discusses the general subject of arteritis, Karsner ³⁴ draws attention to the need for correlation of the views on this type of arterial disease. He states that critical examination of several reports shows that what has been called periarteritis nodosa does not fit the known pathologic or clinical characteristics of this disease. In attempting to clarify the pathologic consideration of arterial inflammation, he proposes the division of these disorders into primary and secondary types. The secondary types of arteritis, he considers,

30 Meves, H. Ueber cerebrale Beteiligung bei der Thrombo-Angitis obliterans (von Winiwarter-Burger'sche Krankheit), *Nervenarzt* **11** 127, 1938.
 Straussler, E., Friedmann, R., and Scheinker, J. Ueber die Endangitis obliterans (von Winiwarter-Burger'sche Krankheit) unter besonderer Berücksichtigung der Hirnveränderungen, *Ztschr f d ges Neurol u Psychiat* **160** 155, 1937.
 Hadorn, W. Ueber Endarteritis obliterans der Organe, *Deutsches Arch f klin Med* **181** 18, 1937.

31 Hausner, E., and Allen, E. V. Thrombo-Angitis Obliterans of the Brain, *Proc Staff Meet, Mayo Clin* **12** 653, 1937.

32 Tartakoff, J., and Hazard, J. B. Thrombo-Angitis Obliterans of the Spermatic Cord, *New England J Med* **218** 173, 1938.

33 Littauer, D., and Wright, I. S. Simultaneous Quadrilateral Acute Ulcerations in Thrombo-Angitis Obliterans. Report of a Case, *Am Heart J* **14** 466, 1937.

34 Karsner, H. T. Primary Inflammation of Arteries, *Ann Int Med* **11** 164, 1937.

are those which are associated with known infectious diseases or are the result of direct extension of inflammation from adjacent foci. In addition to these types he discusses the primary group, which he classifies pathologically into the acute degenerative, necrotizing, exudative, vegetative, proliferative and organizing varieties. In addition to these he recognizes a group of chronic disorders. Most of the examples of arteritis studied were not limited to one of these pathologic characteristics but often included two or more. The vascular phenomena of rheumatic fever are striking examples of this. The arterial inflammation seen in small vessels may be necrotizing or exudative, even proliferative and vegetative changes occur. Chronic arterial changes likewise occur in this condition. In periarteritis nodosa almost all the acute and chronic features of inflammation in the small vessels are present. Proliferative phenomena occur in ergotism. Syphilitic disease of the smaller arteries, he considers, is characteristically exudative and necrotizing. He classifies this as a secondary type of arteritis, this is true of the type seen in tuberculosis, typhus fever and undulant fever.

Horton and Magath³⁵ have made additional contributions to the knowledge of an interesting condition which has been previously reported from the Mayo Clinic and which has been termed arteritis of the temporal vessels. A total of 9 cases have been reported. The pathologic picture somewhat suggests that of periarteritis nodosa except for the absence of aneurysmal sacs. The disease is limited to the temporal vessels. The course in these 9 cases was from four to six months, and complete recovery occurred in each instance. The clinical features were of interest. Headache was an outstanding symptom, being more or less constant and often worse at night. Malaise, weakness, fever and night sweats were usual. These symptoms were often present two to six weeks prior to obvious involvement of the temporal arteries. Pain sometimes was intractable, and difficulty in chewing food was invariably present. Later the temporal arteries became tortuous, large and prominent. Along the course of the vessels reddish, raised nodules were visible and occasionally palpable. In some instances the temporal arteries seemed to become completely thrombosed. In 2 cases phlebitis of the retinal veins was present. It is also interesting to note that all the patients belonged in the older age group, being over 50 years old.

Perlow and Bloch³⁶ report an interesting case of poisoning with ergotamine tartrate, which was administered for the relief of the pruritus of Hodgkin's disease. As the pathogenesis of gangrene in ergot poison-

35 Horton, B. T., and Magath, T. B. Arteritis of the Temporal Vessels. Report of Seven Cases, Proc. Staff Meet., Mayo Clin. **12** 548, 1937.

36 Perlow, S., and Bloch, L. Impending Gangrene of the Feet Due to Ergotamine Tartrate, J. A. M. A. **109** 27 (July 3) 1937.

ing has been considered a primary vascular spasm followed by thrombosis due to stasis and injury of the intima, it was thought by the writers that treatment with papaverine hydrochloride should be effective in halting the progress of gangrene if used before organic vascular changes develop. The fact that this course of treatment was completely successful in preventing the development of gangrene is interesting in view of the mechanism of ergotism.

Puerperal gangrene resulting from the use of ergotamine tartrate is also reported by Benson³⁷

PERIARTERITIS NODOSA

Periarteritis nodosa seems to be attracting more attention. At least it seems to be more frequently reported, and the diagnosis is made during life with greater frequency. The cause of the disease is still unknown. Leishman³⁸ discusses the pathologic picture, and his description fits well the one generally accepted. In his experience the disease occurs most frequently in young males. The complaints are of muscle pain, fever, abdominal pain, edema and weakness. Leukocytosis is usual, and sometimes eosinophilia is present. Tachycardia is out of proportion to the height of the fever. Cutaneous nodules are evanescent, often disappearing within twenty-four hours. The most characteristic lesion is a small nodule fixed in the skin but moving with the deeper tissues. These nodules are painless and occasionally purpuric or vesicular.

Kernohan and Woltman³⁹ emphasize the prominence of neurologic symptoms. Involvement of the peripheral nerves, they say, is especially common. Involvement of the cranial nerves may lead to blindness, diplopia, facial paralysis, deafness and dysphagia. The central nervous system may likewise be involved even to the extent of hemiplegia, delirium or coma. The spinal fluid may be under increased pressure and show an increase in the number of cells and an increased total protein content. They report 5 cases in which the neurologic symptoms were outstanding. The pathologic picture is the same in the cerebral vessels as that which has been described elsewhere.

Kaisner³⁴ points out that critical examination of several reports of the disease shows that what is called periarteritis nodosa does not fit the known clinical or pathologic characteristics of the disease. He has

37 Benson, W. T. Puerperal Gangrene. Report of Seven Cases in Four of Which Ergotamine Tartrate Was Suspected as Being Part Cause, *Tr. Edinburgh Obst. Soc.*, 1936-1937, p. 81, in *Edinburgh M. J.*, August 1937.

38 Leishman, A. W. D. The Clinical Diagnosis of Polyarteritis Nodosa, with Report of Four Recent Cases, *Lancet* **1** 803, 1937.

39 Kernohan, J. W., and Woltman, H. W. Periarteritis Nodosa, *Proc. Staff Meet., Mayo Clin.* **12** 554, 1937.

found that necrosis and exudation are the most frequent types of pathologic change seen in the vessels. In typical cases the cells of the exudate include both polymorphonuclear and mononuclear eosinophils. These cells are not mentioned in many case reports, and their frequency seems to be questionable, but Karsner believes such local eosinophilia to be of great importance in establishing the diagnosis. This finding, together with the other features of the diseases, particularly the nodules emphasized by Klemperer, should make it possible to avoid the inclusion of a wide variety of arterial inflammatory conditions under the term *periarteritis nodosa*.

Brenner⁴⁰ also emphasizes the importance of the cerebral manifestations of the disease.

Sandler⁴¹ reports a case in which there were uremia and sepsis, with milary abscesses in the lungs and kidneys. An unusual symptom was the appearance of ulceration of the mucous membrane of the mouth. Heinrich⁴² observed 1 patient in whom the condition lasted for fourteen years. Vining⁴³ describes an instance of the disease in which the diagnosis was made on the basis of the presence of cutaneous nodules. This patient apparently made a complete recovery.

ARTERIOSCLEROSIS

The relation of altered cholesterol metabolism and the etiology of arteriosclerosis is discussed in several papers.

Menne, Beeman and Labby⁴⁴ state that atheromatous lesions always contain cholesterol, whether in herbivorous or in omnivorous animals. The process in man is comparable with that seen in animals. Any condition which lowers metabolism in man or animals will result in abnormally increased amounts or altered states of cholesterol in the blood and will further its deposition. They believe this to be the essential factor in the production of arteriosclerosis. The disease does not develop in those conditions which tend to deplete the blood of cholesterol. This is demonstrated by the fact that in rabbits fed cholesterol under conditions of increased metabolism, induced by feeding thyroid, the disease fails to develop. These authors agree that the two essential factors in the pro-

40 Brenner, F. Zur Kenntnis der Hirnveränderungen bei *Periarteritis nodosa*, Frankfurt Ztschr f Path **51**:479, 1938.

41 Sandler, B. P. *Periarteritis Nodosa*, Am J M Sc **195** 651, 1938.

42 Heinrich, A. Bericht über einen 14 Jahre lang beobachteten Kranken mit *Periarteritis nodosa*, Ztschr f klin Med **132** 577, 1937.

43 Vining, C. W. A Case of *Periarteritis Nodosa* with Subcutaneous Lesions and Recovery, Arch Dis Childhood **13**:31, 1938.

44 Menne, F. R., Beeman, J. A. P., and Labby, D. H. Cholesterol-Induced Arteriosclerosis in Rabbits, with Variations Due to Altered Status of Thyroid Arch Path **24** 612 (Nov) 1937.

duction of atherosclerosis are hypercholesteremia and mechanical stress. Points of mechanical stress furnish the locations for the deposits of lipid. Once the infiltration of the substance into the tissue spaces and the lymphatic chains of the vessel wall is begun, its accumulation there will serve to produce a vicious circle of destruction, absorption and defensive regeneration. This is in agreement with the conclusions of Leary. Handovsky⁴⁵ also agrees on the role of the thyroid gland.

Davis, Stern and Lesnick⁴⁶ studied the cholesterol and fatty acid content of the blood in a group of patients with angina pectoris of atherosclerotic origin. The average values were found to be definitely higher than in the normal persons studied. There were some individual variations, so that these findings were not always constant. Some of the patients with angina showed a normal cholesterol value, while some of the normal persons showed elevated values. However, in the majority of cases of atherosclerosis there was a definite increase in the cholesterol content of the blood.

Rich and Duff⁴⁷ found that experimental arteriolar lesions having the characteristics of the lesions of arteriolosclerosis and arteriolonecrosis in human beings occur in the tissues adjacent to the site of injection of tryptic enzymes such as pancreatic juice, commercial trypsin and papain. The process develops rapidly, and many lesions occur in as short a time as twenty-four hours. The arterioles show thickening of the wall and narrowing of the lumen when no vascular disease existed previously. They are unable to explain the mechanism of the pathologic change, but they suggest that it may result either from the direct action of the substances on the walls of the vessels or from the action of products of protein decomposition.

Hueck,⁴⁸ in discussing the subject of arteriosclerosis, points out that the term includes several distinct types of vascular disease which he thinks must be separated. He divides the condition into three types. The first he considers as a primary type, with uniform thickening of the wall and fibrous hyperplasia. His second type is characterized by nodular thickening, which he considers secondary to inflammatory disease, such as endarteritis, periarteritis and necrotic arteriolitis, or to granulomatous conditions such as syphilis or rheumatic fever. A similar

45 Handovsky, H. Due rôle de la thyroïde et de la parathyroïde dans le développement de l'arteriosclérose, *Schweiz med Wchnschr* **68** 425, 1938.

46 Davis, D., Stern, B., and Lesnick, G. The Lipid and Cholesterol Content of the Blood of Patients with Angina Pectoris and Arteriosclerosis, *Ann Int Med* **11** 354, 1937.

47 Rich, A. R., and Duff, G. L. The Production of Hyaline Arteriosclerosis and Arteriolonecrosis by Means of Proteolytic Enzymes, *Bull Johns Hopkins Hosp* **61** 63, 1937.

48 Hueck, W. Ueber Arteriosklerose, *Munchen med Wchnschr* **85** 1, 1938.

type of condition may follow toxic damage to the wall or necrosis of the media resulting from vasomotor disorders. The third type is characterized by marked thickening of the wall, with a coincidental nutritional defect, such as the secondary form of arteriosclerosis with preceding lipid or hyaline degeneration followed by calcification.

As the result of his studies in arteriography, Veal⁴⁹ has extended his observations on the pathologic relation of intermittent claudication to the blood supply in arteriosclerosis. He describes the normal vascular pattern as demonstrated by arteriography, without essential variation from that recorded in the review of last year. He has found several patterns of arterial obliteration which vary widely in extent. The presence or absence of symptoms of obstruction depend on the extent of the pathologic process and the presence or absence of an adequate collateral circulation. There may be a marked degree of sclerosis involving the larger vessels, but if the occlusive process has been slow in development and the collateral circulation has kept pace with the occlusion, the circulation may be adequate, and no subjective symptoms will occur. He was able to divide the cases of intermittent claudication into three groups. In the first, consisting of 21 cases, there was complete obstruction at some point of one of the large arterial trunks. In the second group, consisting of 6 cases, there was definite, marked narrowing of the lower portion of the femoral or popliteal artery. The constriction was uniform in some, while in others there were large atheromatous plaques protruding into the lumen. The collateral circulation in these cases varied considerably, and in some instances the collateral vessels extended the whole length of the extremity. However, small branches to the muscles were few, although the blood supply was adequate to maintain the nutrition of the extremity. In the third group, consisting of 14 cases, the large vessels of the extremity were patent throughout their course, and their lumens were normal or nearly so. The defect in this group was in the small branches distributed into the muscles. They were few, irregularly placed and shorter than normal. There was marked diminution in the number of fine terminal branches. The obstruction in this group was in the small vessels supplying blood to the muscles, and it is presumed that the arterioles and capillaries were likewise involved. The single abnormality common to all three groups was the obstruction of the small branches to the muscles, with their fine terminal arteriolar and capillary arborization. This was the only abnormality noted in the third group, but it was also present in the first two.

As the result of treatment when improvement was taking place, further arteriographic studies showed no change in the large vessels, but

⁴⁹ Veal, J. R. The Pathological Basis for Intermittent Claudication in Arteriosclerosis, *Am Heart J* **14** 442, 1937.

an increase in the number and in the size of the terminal branches to the muscles was invariably noted. Cases have been described in which there was obstruction of the popliteal artery, with gangrene of the foot, and in which intermittent claudication was not present. In such instances the supply of the small branches to the muscles was adequate. Veal also comments on the fact that the integrity of the muscle cells in such conditions remains unimpaired because they receive sufficient nutrition by way of the tissue spaces from either the venous or the arterial side of the circulation. So it is only in instances of extreme involvement that necrosis of muscle tissue may be expected actually to occur.

Bernheim and London⁵⁰ comment on the similarity of the symptomatology in obliterating arteriosclerosis and in thromboangitis obliterans. The decreased peripheral blood supply in both diseases is due in part to organic changes in the vessel walls which cause them to be obliterated or narrowed and in part to functional vasoconstriction. Vasospasm, they believe, is a factor of as much importance in arteriosclerosis as it is in thromboangitis obliterans except in the advanced cases, in which the walls of the vessels are too rigid to respond. The vessels of the extremities are unduly sensitive to vasoconstricting influences, such as exposure to cold, the use of tobacco or a deficient diet. Vasoconstriction in such cases is prolonged beyond the normal response in more or less continuous vasospasm. They found an increase in the viscosity of the blood in arteriosclerosis as well as in thromboangitis obliterans. The patients with arteriosclerosis respond as well or better to treatment than do those with thromboangitis obliterans. Their methods will be discussed under the subject of therapy.

Veal,⁵¹ in discussing the various factors in the mortality rate in cases of arteriosclerotic gangrene, points out the importance of considering this disease not from the standpoint of local peripheral involvement alone, but in view of the fact that it is a systemic disease, which implies generalized vascular deficiency. All the vessels of the body are likely to be involved, from the thoracic aorta to the terminal branches. In dealing with arteriosclerotic gangrene the effects of the disease on the heart, kidneys and other vital organs must be considered as well as the local complications of infection and gangrene. He states that the arteriosclerotic subject manifests the same susceptibility to infection as does the diabetic patient, although in a more sluggish manner. Infection is often deep seated and spreads along the tissue planes, possibly not

50 Bernheim, A. R., and London, I. M. Arteriosclerosis and Thrombo-Angitis Obliterans. Report of Cases and Treatment, *J. A. M. A.* **108** 2102 (June 19) 1937.

51 Veal, J. R. Factors in the Mortality Rate of Arteriosclerotic Gangrene. A Comparative Study of Two Hundred and Fourteen Cases of Surgical Intervention, *J. A. M. A.* **110** 785 (March 12) 1938.

becoming manifest in a true line of demarcation. If infection is not actually present with gangrene, it is always potentially present. Infection increases gangrene, and gangrene increases infection exactly in the same manner as they do in the diabetic patient. However, the constitutional reaction in the arteriosclerotic patient may not be so marked as in the diabetic. The patient is often listless and drowsy and sometimes stuporous and may show mild senile dementia. He may refuse food and fluid and is often indifferent to his surroundings. Such general symptomatic factors are of the utmost importance when surgical treatment is being considered.

Instances of youthful development of arteriosclerosis have been occasionally reported. Such a case is reported by Thomasen,⁵² who describes the condition in a child of 8 years.

CONGENITAL ARTERIOVENOUS COMMUNICATIONS

Seeger⁵³ has published an excellent paper in which all types of normal and abnormal arteriovenous communications are discussed and the literature is reviewed. The characteristic physiologic and pathologic aspects of normal arteriovenous anastomoses and abnormal arteriovenous fistulas are reviewed in detail. Much of this material has been considered in previous reviews.

In discussing arteriovenous fistula the essential characteristics are considered by the writer. They are sufficiently important to be repeated here. There is a high admixture of arterial and venous blood in the regional or deep veins of an extremity. The local effects are those manifested by the abnormalities of the vessels themselves. The vein below the point of the anastomosis is dilated by the increased volume of blood contained in it. This results in a pressure greater than that which the vein is capable of withstanding. As a result the vessel becomes dilated and tortuous. The larger the fistula and the longer its duration the more widespread is the venous involvement. The involved artery shows a thinning of its walls. It becomes dilated, and degenerative changes in all its coats take place proximal to the fistula. This varies with the extent of the fistula.

The regional effects are the changes which occur in the limb affected. The first is hypertrophy, shown by an increase in the size of the extremity, not only in circumference but occasionally in length in the case of congenital communications. There is an increase in surface temperature, and trophic changes frequently occur. The latter are

52 Thomasen, E. Arterienverkalkung bei einem 8-jährigen Knaben. Nach Behandlung mit Vitamin-D². *Acta med Scandinav* 95:505, 1938.

53 Seeger, S. J. Congenital Arteriovenous Anastomoses, *Surgery* 3:264, 1938.

probably due to the diminution in the flow of blood through the capillaries because of the much greater volume of blood passing through the abnormal communication. The increased pressure in the veins impedes the return of deoxygenated blood from the capillaries. Consequently a state of anoxemia becomes chronic in the distal portion of the extremity. Bruits and thrills may be found. The general or symptomatic features of the condition depend on the disturbance in function of the circulatory system produced by the fistula. Because the fistula short circuits the blood away from the capillary system, a decrease of peripheral resistance results. As a consequence there is often a reduction in diastolic blood pressure with an increase in pulse pressure. The total volume of circulating blood is said to be increased. This is particularly true when there is a large fistula. Cardiac enlargement has been frequently noted, and sometimes symptoms and signs of cardiac failure have been recorded. This condition of the heart is not merely a coincident abnormality but is consequent on the fistula. The author quotes Leiche, who excised a large arteriovenous aneurysm from a patient who had cardiac decompensation and considerable cardiac enlargement. The heart returned to normal size, and signs of decompensation disappeared after the operation. The reason for the detrimental effect on the heart produced by the presence of abnormal arteriovenous communications is obscure. It seems reasonable to believe that there are three factors which may take part in this effect. One is the augmented filling of the right ventricle, dependent on the abnormal escape of blood directly into the veins. The left ventricle is called on to increase its output in order to maintain the general blood pressure. It is questionable whether this actually occurs. The total increased blood volume may be a still more important factor. Another interesting finding in cases of this kind is the slowing of the heart, which has been spoken of as Branham's phenomenon. In the cases which Seegar reports, infia-red photography proved to be an important aid in the differential diagnosis of hemihypertrophy. Arteriography was not of great help in his cases in locating the abnormality.

Horton and Baldes⁵⁴ have employed the electric stethophone with a recording device to differentiate the murmurs of peripheral aneurysm and arteriovenous fistula. The murmur of the former is typically systolic as to time, while the latter is characterized by a more nearly continuous murmur which has systolic accentuation. It is sometimes difficult to detect these differences with the unaided ear. A graphic record of the

54 Horton, B. T., and Baldes, E. J. A Photographic Method of Recording Bruit. A Means of Differentiating Aneurysm and Arteriovenous Fistula, Preliminary Report, Proc. Staff Meet., Mayo Clin. **12** 823, 1937.

vibrations produced by such abnormalities serves to differentiate them not only as to differences in time with relation to the cardiac cycle but also as to recorded differences in vibratory rate

GLOMUS TUMOR

Stabins, Thornton and Scott⁵⁵ have made some additional studies of this interesting condition. They point out particularly the derangement of the vasomotor mechanism, which is a typical feature of the disorder. The clinical pictures in the 2 cases reported are characteristic. There are mainly phenomena of vasodilatation. The vascular relaxation which occurs in these cases is probably the result of a reflex arc which extends at least back to the spinal cord or possibly to the sympathetic ganglions. The symptoms of vasodilatation endure for as long as eight weeks after operation for removal of the growth, as evidenced by the persistence of some discomfort in the region of the excised tumor. The phenomenon of pain observed in erythromelalgic states may have a similar reflex origin. The writers suggest that pain itself may be the efferent stimulus which produces the vasomotor response.

POPLITEAL ANEURYSM

Theis,⁵⁶ in reporting 5 cases of popliteal aneurysm emphasizes the consideration of this condition in all cases of unilateral peripheral circulatory disorder. This is true because the peripheral manifestations may occur before the onset of local symptoms in the popliteal space.

Arterial pressure is partially expended in dilating the aneurysmal sac. A reduction in pressure in the distal circulation occurs. The peripheral arterial pulsations and temperature are then reduced. With muscular activity or with vasoconstriction from exposure to cold, peripheral resistance increases. A still greater dilatation of the aneurysmal sac then results. Because of the location of the popliteal aneurysm deep in the popliteal space, early diagnosis on the basis of local findings is often difficult.

Theis has found that oscillometric curves show three distinctive features characteristic of the aneurysm. There is an increased height of the curve above the normal limits in the region of the disorder. There is absence of normal distal reduction in height from the thigh to the ankle. Finally, there is fluctuation in the height of the curve as the result of

55 Stabins, S. J., Thornton, J. J., and Scott, W. J. M. Changes in the Vasomotor Reaction Associated with Glomus Tumors, *J. Clin. Investigation* **16** 685, 1937.

56 Theis, F. V. Popliteal Aneurysms as a Cause of Peripheral Circulatory Disease, with Special Studies of Oscillomographs as an Aid to Diagnosis, *Surgery* **2** 327, 1937.

peripheral vasoconstriction or dilatation. Strenuous muscular exercise or vasoconstriction in the foot and leg as the result of exposure to cold was found to be associated with greatly increased oscillations in the aneurysmal sac.

EMBOLISM AND THROMBOSIS

Although the clinical features of these disorders are quite well known, several papers have appeared which correlate the findings and, as a result of increased experience, emphasize variations in the clinical features of these conditions.

Graham⁵⁷ discusses the etiology of arterial thrombosis and emphasizes the importance of the recognition of previous arterial and myocardial diseases with varying degrees of insufficiency of both the heart and the peripheral arteries. Damage to the lining of the vessels and slowing of the circulation as the result of myocardial impairment seem to be the most important etiologic factors of both disorders. Embolism is more frequent in the larger arteries than is thrombosis. There were 34 cases of embolism, with 14 cases of thrombosis.

Rykert and Graham⁵⁸ describe pain of two distinct types occurring in cases of arterial embolism. The first is that usually described. It is sudden and severe and is localized in the region of obstruction. This is followed by numbness and later by coldness. These later symptoms begin at the distal end of the extremity and extend upward to a point a little below the site of occlusion. After a time the original acute pain subsides and is often followed by severe pain in the area of numbness and coldness. Other signs of impaired arterial circulation are also present. These writers, in agreement with others, state that an embolus tends to lodge at a major bifurcation of one of the peripheral arteries. The lower extremities are involved more frequently than are the upper. In the leg the common femoral artery is most often occluded and in the arm the brachial artery. Both branches at the bifurcation may be occluded, or there may be complete occlusion of one and partial occlusion of the other. "A sudden development of numbness in one leg and tingling or numbness in the other point to embolism at the bifurcation of the aorta causing complete occlusion of the common iliac on one side and partial occlusion on the other."⁵⁷ If numbness is followed by tingling, this is an indication of a return of blood flow in the extremity. The pain with the occlusion of the aorta is usually referred to the back, whereas that of the iliac artery is referred to the abdomen. Occasionally embolism in this region may

⁵⁷ Graham, D. Embolism and Thrombosis of the Larger Arteries. Their Diagnosis and Treatment, *Canad. M. A. J.* **36** 33, 1937.

⁵⁸ Rykert, H. E., and Graham, M. G. Some Problems in the Diagnosis, Prognosis and Treatment of Acute Arterial Occlusion, *Am. Heart J.* **15** 395, 1938.

cause acute pain referred to the thigh, and occasionally acute pain develops in the lower part of an extremity after occlusion higher up. This may indicate that a fragment of an embolus has broken loose and secondary embolism has occurred in another distal location. The primary localization of an embolism is best determined by the location of the original acute pain or of the first bifurcation of the main artery above the upper limit of numbness and coldness.

In differentiating thrombosis from embolism Graham states that the clinical pictures of these two disorders are very similar. Thrombosis of a larger artery is not characterized by the sudden onset of pain, as is the case usually with embolism. A gradual rather than a sudden onset of numbness is characteristic of thrombosis. The presence of the etiologic factors necessary for the development of these conditions must always be considered. Thrombosis commonly results from infection, trauma, thromboangitis obliterans or arteriosclerosis. In regard to the occurrence of pain as an initial symptom of embolism, Rykert and Graham found it present in 64 per cent, and in the later stages it was present in all their cases.

Pain is not always a prominent symptom. Numbness and tingling or motor paralysis may precede the pain by several hours. De Takáts⁵⁹ also points out in a recent paper, as he has before, that embolism may appear to be gradual in onset, with minor symptoms due to the appearance of small particles of a cardiac thrombus in an extremity before the main embolism occurs. Rykert and Graham state that when pain occurs at the onset and is referred to the level of the occlusion, this always precedes numbness and coldness. This pain is of short duration, lasting for only a few minutes, and is succeeded by prolonged distress or pain in a lower portion of the extremity in association with numbness and coldness. This temporary pain is not due to ischemia but is probably due to spasm at the site of the embolus, in their opinion. They believe that pain distal to the site of occlusion which develops later is due to ischemia. De Takáts shares this view. In some of his cases pain has been entirely absent. The absence of pain in acute embolism has been discussed by Allen. De Takáts states that thrombosis may occur so suddenly that it may be the initial symptom of widespread arterial disease. This may be the case in either arteriosclerosis or thromboangitis obliterans. The infrequency of gangrene after an embolus has lodged in the upper extremity is also pointed out. The collateral circulation is usually adequate to maintain the tissue integrity. De Takáts finds thrombosis indistinguishable from embolism and states that multiple arterial thromboses, because of their multiplicity, may

⁵⁹ de Takáts, G. Vascular Accidents of the Extremities, *J A M A* **110** 1075 (April 2) 1938

simulate embolism. In discussing thrombosis and postoperative embolism, Bancroft and his associates state the belief that there must be some biochemical change in the blood which precedes or accompanies thrombophlebitis. While this is no doubt true in postoperative embolism, it is also probable that in peripheral embolism some similar alteration may occur. The factors favoring the production of thrombosis are still obscure.⁶⁰

McKechnie and Allen⁶¹ have studied the effect of the mechanical occlusion of individual arteries of an extremity. No pain was observed except that resulting from local pressure of the device used to obstruct the vessel. Arteries were occluded for as long as thirty minutes. The effect of such compression on the circulation of an extremity was not usually great. This is in sharp contrast to the results in cases of acute embolism. They agree that the pain which occurs in cases of embolism is due not to mere occlusion of a vessel but to the ischemia which results from a diffuse spasm involving the vessels of the extremity.

ANGIOSPASTIC DISTURBANCES

Of the group of vasospastic disorders, the most variable are those due to lesions of the central nervous system.

Pinkston and Rioch⁶² report experimental studies on the ablation of cortical areas in the monkey. In general, their findings are in agreement with those of previous workers. The criterion for the determination of vasoconstriction was a decrease in the cutaneous temperature of the palms or of the soles. This decrease of cutaneous temperature was on the side opposite the lesions made in areas 4 and 6 (Brodman) of the cerebral cortex. This decrease in temperature as compared with that of the opposite side persisted for as long as six months. They conclude that central mechanisms which control vasomotor reactions are localized in these areas. The mode of control and the pathways of conduction as well as the subcortical centers involved are obscure.

Allen and Craig⁶³ report an interesting case of tumor of the spinal cord in which the presenting symptoms and physical findings suggested impairment of arterial circulation of an organic type. They

60 Edwards, E. A. Observations on Phlebitis, *Am Heart J* **14** 428, 1937.

61 McKechnie, R. E., and Allen, E. V. Effect on the Circulation of Mechanical Occlusion of Individual Arteries of the Extremities. Relation to Arterial Embolism, *Am Heart J* **14** 127, 1927.

62 Pinkston, J. O., and Rioch, D. M. The Influence of the Cerebral Cortex on Peripheral Circulation, *Am J Physiol* **121** 49, 1938.

63 Allen, E. V., and Craig, W. M. Vascular Clinics. III. Effect of Lesions of the Nervous System on Circulation, Report of a Case of Spinal Cord Tumor Which Produced Disturbances of Circulation, *Proc Staff Meet, Mayo Clin* **13** 131, 1938.

point out that a variety of neurologic lesions, varying from simple disuse of a member to hemiplegia and other central lesions, may produce rather striking peripheral vascular phenomena. Whenever the symptoms of suspected vascular disease are unusual or the findings on physical examination do not explain the symptoms adequately, a lesion of the central nervous system to which the disturbances of circulation are secondary may be suspected.

Heinbecker and Bishop⁶⁴ discuss the mechanism of the Raynaud syndrome under the title of spastic vascular disease. They do not subscribe to the view that this condition is the result of hyperfunction of the sympathetic nervous system. In fact, they point out that conditions in which hyperfunction does exist are not associated with the Raynaud syndrome. The fact that the paroxysm may be initiated by emotional excitement as well as by exposure to cold is easily explained by considering that the mechanism of constriction is a combined reflex and humoral one. Cold produces a reflex excitation of vasoconstrictor impulses to the blood vessels and also reflexly produces an increased secretion of epinephrine. Emotional activity is expressed through motor impulses over the sympathetic nervous system which affect blood vessels, sweat glands and the pilomotor mechanism and, in addition, produce increased secretion of epinephrine. They believe that reflex activity of the autonomic nervous system is a definite factor in the development of an attack. In normal persons on exposure to cold there is a reflex constriction of blood vessels. This is due not only to a primary local somatic reflex but in part to a generalized response characteristic of autonomic reflexes. They do not believe that this reflex response in persons with spastic vascular disease is any different from that in the normal person but that there is a definite quantitative increase in the response. They were able to induce the typical paroxysm by the subcutaneous injection of epinephrine hydrochloride or 10 to 15 units of insulin even in a warm room. Such an induced attack could be relieved by the administration of 20 per cent solution of dextrose intravenously. They explain that the same type of reaction occurs in patients with the Raynaud syndrome in response to the injection of epinephrine hydrochloride as to exposure to cold. This occurs in persons whose sympathetic nervous system is intact. This reaction to epinephrine is similar to the increased response in denervated vessels. The cause in their opinion is to be regarded as a constitutional change in the walls of the blood vessels which makes them respond more than normally to a normal vasoconstrictor impulse and to circulating epinephrine. Cold itself plays a minor role as a direct constrictor agent in the typical spasm. It is merely the stimulus.

64 Heinbecker, P. and Bishop, G. H. The Mechanism of Spastic Vascular Disease and Its Treatment. *Ann. Surg.* 107: 270, 1938.

Several cases of spasm of the retinal artery⁶⁵ have been reported in association with the Raynaud syndrome. Such a case is that cited by Carpenter and Carpenter⁶⁶. In spite of rather pronounced vasoconstriction, the retina showed no evidence of organic damage.

Under the term angiospastic claudication Pearl⁶⁷ reports a group of cases in which pain of the type characteristic of intermittent claudication was the outstanding symptom. He states that organic disease was excluded in the entire group. However, this condition may occur without any evidence of organic vascular disease or as an early manifestation of organic disease before obstruction has become sufficient to cause the condition. In this connection it is interesting to note that some of Veal's patients had an apparently intact arterial blood supply into the foot when the small vessels to the muscles could be shown by arteriography to be impaired.

Junghanns,⁶⁸ in discussing impairment of blood vessels due to the use of pneumatic tools, describes the usual picture but, in addition, states that in some cases the spasm may become so severe that death of local tissue may result. In 1 case there were pathologic signs with occlusion of small vessels somewhat similar to that seen in thromboangitis obliterans.

De Takáts⁶⁹ again draws attention to a peculiar and poorly understood condition under the heading reflex dystrophy of the extremities. It has been described previously under a variety of names, such as post-traumatic osteoporosis, chronic traumatic edema, traumatic vasospasm, Sudeck's acute atrophy of bone and the like. The manifestations of this syndrome are rather diverse, and many of the preceding reports are based on a partial consideration of the condition. The vasomotor phenomena are often prominent at first but later may be overshadowed by the development of trophic symptoms. Hard, nonpitting edema is usually present but sometimes is not sufficiently outstanding to attract attention. Osteoporosis is usually present, and a picture of an irregular spotty atrophy of bone is shown roentgenographically. The condition resembles in some respects the atrophy of disuse. The edema is

65 Wauters, M. L'artère rétinienne dans la maladie de Raynaud, *Bull. Soc. belge d'opht.*, 1937, no. 74, p. 27.

66 Carpenter, W. M., and Carpenter, E. W. Raynaud's Disease with Intermittent Spasm of the Retinal Artery and Veins. Follow-Up Report of a Case, *Arch. Ophth.* **19**: 111 (Jan.) 1938.

67 Pearl, F. L. Angiospastic Claudication, *Am. J. M. Sc.* **194**: 505, 1937.

68 Junghanns, H. Impairment of Blood Vessels by Continuous Concussions as a Result of Work with Pneumatic Tools, *Arch. f. klin. Chir.* **188**: 466, 1937.

69 de Takáts, G. Reflex Dystrophy of the Extremities, *Arch. Surg.* **34**: 939 (May) 1937.

accompanied by pain, usually of paroxysmal type. The extremity is sensitive to changes in temperature and is particularly sensitive to superficial or deep pressure. There are no definite sensory changes, but ill defined hypesthesia may be present. The muscles are first hypertonic, owing to a reflex increase in irritability, but later become atonic. Early in the course of the disorder the temperature of the skin is higher than that of the normal side and later often lowered. Profuse sweating may occur. Trophic changes appear later. The nails become brittle and ridged. Eczema may occur, and herpetic lesions have been described. The skin may be glossy and bluish. The bone shows the characteristic spotty atrophy, which may become diffuse in the later stages. The capsules of the joints shrink. Movement of the affected joints becomes painful. Contractures may occur. Oscillometric studies show first an increase and later a decrease in the height of the curve. The hyperemic reaction to cold is delayed, and when it appears it endures much longer than normally.

This condition seems most frequently to follow mild trauma of various types, low grade infection, slight injury to a nerve, a burn or a frostbite. It probably occurs frequently but usually subsides before striking or intractable symptoms develop. In the rarer cases long-continued disability occurs and may even become complete. Pain has been so severe in cases of this type that amputation has been performed.

De Takáts states that in persons in whom the disorder occurs with maximum severity, constitutional inferiority is unmistakable. Emotional disturbances often aggravate the clinical symptoms. The disorder must be differentiated from functional neurologic states with atrophy from disuse. In addition the condition often resembles edema of venous or lymphatic origin, inflammatory conditions involving the bone or tendons, injuries and in the lower extremity spasmodic flatfoot.

The writer regards as the most important feature of this condition an exaggeration of a nutritional reflex, which is set up by the original injury or infection, which does not subside when the effect of the exciting cause disappears. It becomes a "fixed self perpetuating mechanism in which catabolic (destructive) activities are predominating."

This reflex is actuated by a chronic focus of irritability in the periphery. This produces a weak continuous stimulation through the ordinary sensory pathways to the cord, with relay to the lateral horn, and from here an efferent sympathetic impulse to the tissues follows. In 3 of the 5 cases reported by the author, all of the intractable type, this reflex was controlled by excision of the irritable focus. Sympathectomy completely relieved the condition in 1 case, and block of the sympathetic ganglions with procaine hydrochloride temporarily relieved the symptoms in another.

ACROCYANOSIS

After a study of a large number of cases of acrocyanosis, Stern⁷⁰ is of the opinion that this is a clinical disease entity the cause of which is frequent moderate cooling of the affected parts in conjunction with chilling of the body as a whole. Its mechanism is partial obstruction of the arterial blood supply of the skin of the hands and feet. He found no evidence of venous obstruction. In his opinion the site of the obstruction is in the arterioles of the skin and subcutaneous tissue. It is not merely arteriolar spasm, but there is actually an increase in the muscular tissue of these vessels. He states that there is no evidence of abnormality in the blood, central nervous system or glands of internal secretion. The successful treatment in such cases is continued warmth without exposure to cold for a period of months. These views are decidedly at variance with those of most observers.

A complete and careful study of a case of unusually severe acrocyanosis has been reported by Lambie and Morison.⁷¹ In association with their study of this case they present a most exhaustive and careful discussion of the various manifestations of the symptom complex and the mechanism of the production of symptoms. Their patient showed the typical circulatory manifestations to a rather marked degree. She was a young woman of subnormal intelligence, so that she was unfit for any occupation. She was likewise physically defective, although no definite diagnosis of her condition was recorded. It seems that some endocrine disorder was at least a coincident if not an etiologic factor in the patient's condition. They found the vascular defect to be an obstruction in the smaller vessels in the hands and feet, either the arterioles, the arteriovenous anastomosis or the subpapillary arteriolar plexus. They thought all the vessels might be involved. In addition to the arteriolar constriction, capillary dilatation was found to be present. They believe that the capillary dilatation was probably dependent on the arteriolar constriction.

Their findings, in general, correspond well with the views of Lewis and Landis, as reported in a previous review. By means of nerve block with procaine hydrochloride they were able to obtain release of the arteriolar spasm, as were Lewis and Landis, but in their patient the change in color was observed before there was a rise of temperature in the surface structures. This is contrary to the findings on which Lewis and Landis based their conclusions.

No change in the temperature of the limbs followed the injection of acetylcholine. Injection of histamine phosphate intramuscularly was fol-

⁷⁰ Stern, E. S. *Acrocyanosis*, *J. Ment. Sc.* **83** 408, 1937.

⁷¹ Lambie, C. G., and Morison, S. M. *Acrocyanosis*, *M. J. Australia* **2** 1070 1937.

lowed by flushing of the skin of the hands and feet without any rise in temperature. This reaction, they felt, was due to the general vasodilatation, which diverted much of the flow of blood to the deeper structures. When histamine was picked into the skin of the affected area, no wheal was formed, but a more extensive flare appeared than in the normal skin. They interpret this as indicating that the arterioles reacted promptly and fully to histamine. Once they have relaxed, cyanosis disappears. There was no evidence of structural change in the arterioles. The fact that the flare was irregular and of greater extent than in the normal areas could be accounted for by the relaxed state of the capillaries and venules of the subpapillary plexus. The flare persisted for an unusually long period. This, they felt, was due to stasis in the capillaries. The local effect of epinephrine hydrochloride in blanching the skin illustrated normal ability of the arterioles and capillaries to contract. Solution of posterior pituitary, which acts almost exclusively on the capillaries in the human skin, produced a pale area of the same type as that seen in the normal subject. When it was injected intramuscularly, the type of reaction in the cutaneous vessels was normal except that the pallor in the hands was patchy and irregular. The writers have been unable to satisfy themselves as to whether or not the actual defect is local in the vessels or of central origin. They incline to the latter belief but can offer no direct evidence for its support. The fact that the vascular change is confined to the exposed parts, from which the loss of heat is greatest, especially the distal portion of the extremities, suggests that the defect lies in the central control of the vascular mechanism concerned with the regulation of body temperature or with the adaptation of vasomotor tone. The hypothesis of endocrine dysfunction as a cause of acrocyanosis did not appear to explain satisfactorily all the features presented in this case, although the clinical picture suggested in many respects that of Simmonds' pituitary cachexia. The authors point out that acrocyanosis may be confused easily with the Raynaud phenomena, in fact, they are inclined to believe that a number of cases reported in the literature should be classed in this group.

PHLEBITIS

Phlebitis is a type of vascular disease about which there has been considerable uncertainty. Edwards⁶⁰ has attempted to correlate information on this subject. He divides the cases into two major groups, those of suppurative and those of nonsuppurative or bland phlebitis. Suppurative phlebitis is seen in the immediate vicinity of a purulent focus. The involved vein may show no more clinical signs of inflammation than the nonsuppurative form. The clot is infected and undergoes purulent softening, and bacteria and portions of the clot may be dis-

seminated throughout the blood stream. Bacteria are invariably found in the involved portion of the vein and its contained clot. The non-suppurative type of phlebitis is that usually seen postoperatively. This phlebitis also occurs in cases of fevers and of terminal states, as well as in cases of varicose veins. The involved vein shows the signs of inflammation often augmented by edema resulting from interference with the return circulation. The presence of bacteria in conditions of this kind is controversial. In many instances bacteria cannot be demonstrated, while in some instances infection no doubt is an important factor in producing the inflammatory process. It may be due to alteration in the character of the blood or to slowing of the blood stream. This is in distinct contrast to the definite findings in septic thrombophlebitis.

The histologic reaction consists of the so-called chronic inflammatory or reparative processes, with infiltration of lymphocytes and plasma cells. Polymorphonuclear leukocytes are uncommon. The infarct resulting from this type of phlebitis does not give rise to abscess formation. As a consequence of any type of phlebitis, irritation or stimulation of the sympathetic nerve fibers may take place. Whether by direct irritation or by reflex from the wall of the vein there is adequate stimulation for the production of vasospasm. This may take the form of vasoconstriction involving the vein itself or the adjacent small veins of the extremity or may induce a pilomotor reflex or even localized sweating.

More important than these reactions is the arterial constriction which may occur as the result of sympathetic irritation. This reaction may vary from a lowering of temperature, best accounted for by arteriolar constriction, to severe and complete spasm of a major artery of an extremity. The picture may closely resemble that of arterial embolism. The femoral vein is most frequently involved, and in this instance the condition is usually secondary to thrombophlebitis of the femoral or iliac vein. The condition may be ushered in by sudden severe pain along the course of the artery and later in the entire leg. Pulsation of the femoral artery is absent and the extremity cold and immobile. After a few hours the condition may disappear spontaneously, but actual thrombosis has been known to occur.⁷² When the phlebitis has been previously noted, the condition is more readily recognized, but it often happens early in the course of venous involvement, so that the differential diagnosis is rendered difficult. Often the only indication of primary venous involvement is slight cyanosis above the area of ischemia and some dilatation of the surface veins. The number of such

⁷² Pringle, J. H. Massive Ischaemic Gangrene with Thrombosis of Veins and Patent Arteries, Glasgow M. J. **129** 126, 1938.

cases reported has steadily increased⁷³ The persistent disability after thrombophlebitis has been the subject of an investigation by Edwards and Edwards⁷⁴ They have found that the inflammatory process involves the valves of the veins in various ways, so that the cusp is damaged or completely destroyed The destruction of the valve or its damage results in insufficiency, so that the return flow of blood in the extremity is retarded Even though the vein may be recanalized and the lumen adequately restored, the circulation becomes inadequate because of the incompetence of the valves in the vein or in the adjacent collateral channels The valves in the collateral veins may be damaged, because these vessels become greatly dilated The end result is permanent chronic impairment of the circulation in the extremity

Edwards and Edwards⁷⁴ consider thrombosis of varicose veins to be due to factors other than infection, although they recognize the possibilities of latent infection These factors are slowing of the blood stream, physical and chemical changes in the blood and alterations in the endothelial lining of the vessels

The thrombotic process may begin spontaneously or follow some incident It may vary from a chronic to an acute process and may be of long or short duration It is often recurrent It is most common in the superficial veins, through which it extends in both directions Occasionally it remains localized but may extend to the deep veins of an extremity

Pulmonary infarcts seldom occur from thrombosis in varicose veins if the patient is ambulatory, because with the impairment of the venous valves the hydrostatic pressure is sufficiently great to prevent escape of the clot through the saphenous vein, consequently it becomes more securely anchored in its original location This is not true if the patient is confined to bed

In addition to the usual factors which produce thrombosis, the possibility of alteration in the process of coagulation has been considered⁷⁵ High clotting indexes were found in a number of cases Prophylactic treatment instituted in a group of these was entirely successful while in a control group the average number of accidents occurred Heparin is a satisfactory prophylactic⁷⁶

73 Lindgren, S Arterien-Symptome bei den tiefen Bein thrombosen, Upsala lakaref forh **42** 415, 1937

74 Edwards, E A, and Edwards, J E The Effect of Thrombophlebitis on the Venous Valve, Surg, Gynec & Obst **65** 310, 1937

75 Edwards, E A Thrombophlebitis of Varicose Veins, Surg, Gynec & Obst **66** 236, 1938

76 Bancroft, F W, Brown, M S, and Chargaff, E Postoperative Thrombosis and Embolism, Ann Surg **106** 868, 1937

PRIMARY VASCULAR HYPERTENSION

It is intended in this discussion not to review the subject of hypertension but merely to include briefly a few contributions concerned with the etiology of this important disorder. The hypertension of renal disease has been considered in a previous review⁷⁷. It is obviously impossible in the light of present knowledge to separate essential hypertension from that of renal disease entirely.

Much of the present interest in this disorder has resulted from attempts to relieve its symptoms by means of operations on the sympathetic nervous system. This, in turn, has been the outgrowth of the surgical procedures applied to relieve the peripheral vasoconstrictor phenomena of Raynaud's disease and other vasospastic conditions.

The rationale of such a procedure is based on the assumption of the existence of increased tonus in the whole or in a part of the peripheral arteriolar system mediated by some central mechanism. That reflexes of peripheral origin or central impulses have an effect on blood pressure cannot be doubted, but that essential hypertension is of central nervous origin is exceedingly doubtful. Whether the essential cause is on this basis, that of impaired circulation of blood to the renal tissue or the result of an increased response to endocrine hormones, or a combination of these factors, still remains uncertain. Regardless of the obscurity of the cause, definite advances in understanding of this condition have been made, and it seems probable that the work of Goldblatt and his associates will prove to be the foundation on which the future knowledge of the subject will be based.

In a recent paper, which in part constitutes a review of this splendid work, Goldblatt⁷⁸ discusses the pathogenesis of experimental hypertension induced in animals by his method. He states that the results of experiments in which hypertension due to renal ischemia has been produced in dogs indicate that the mechanism of this type of hypertension is primarily a humoral mechanism of renal origin. These experiments indicate the importance of the reduced flow of blood to the functioning components of the kidneys as the primary cause of this type of hypertension and perhaps of the type of primary vascular hypertension observed in man which is associated with arteriolar disease of the kidneys. He suggests that the improvement which has been reported to result from operation on the sympathetic nervous system in many instances may be due to the improvement of circulation which is effected

77 McCann, S. W. Bright's Disease. A Review of the Recent Literature, *Arch. Int. Med.* **61**: 501 (March) 1938.

78 Goldblatt, H. Studies on Experimental Hypertension. V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann. Int. Med.* **11**: 69, 1937.

through the kidney and not by a direct effect on the vasomotor mechanism of the splanchnic vessels. That the mechanism of experimental hypertension is humoral, involving a hypothetic substance of renal origin, is a theory based on only indirect evidence. Bilateral nephrectomy or complete occlusion of the renal arteries is not followed by hypertension. This is interpreted as being due to the absence of the hypothetic effective renal substance when the kidneys are absent. If circulation to the kidneys is completely shut off, the effective substance cannot enter the circulation. The cortex of the adrenal gland may play an important part in the development of this type of hypertension, while the medulla has no effect. Complete bilateral removal of the adrenal glands without substitution therapy has interfered with the development of this type of hypertension. The exact way in which the hormone of the adrenal cortex acts in conjunction with the hypothetic renal substance in the development and maintenance of hypertension has not been demonstrated.

The work of Goldblatt and his associates has definitely established that hypertension can be produced in experimental animals by the maintenance of renal ischemia. Hypertension of this type closely resembles the benign and malignant types seen in man. The severity of this hypertension and the coincident presence of impairment of renal function or its absence apparently depend on the degree of constriction of the renal arteries. The hypertension thus produced may be a general reflex arising from the kidneys or the result of some humoral substance elaborated by the kidneys. The evidence is preponderantly in favor of the latter view. It seems also to be true that the hormone of the adrenal cortex is in some way associated with the development of this type of hypertension. The work of Goldblatt has been confirmed by a number of investigators.

Harrison and his associates⁷⁹ have made some interesting observations on the effects of extracts of the kidneys of normal dogs and of dogs with hypertension induced by interference with the flow of blood through the renal arteries on the blood pressure of rats. They were able to demonstrate a rise in blood pressure in rats after the administration of saline extracts of the kidneys of normal dogs. Extracts of the kidneys of dogs in which hypertension had been induced caused a marked increase in blood pressure. There was a much greater pressor effect noted from the extract of one kidney in which ischemia had been produced in comparison with that of the other kidney of the same animal in which the renal circulation was normal.

⁷⁹ Harrison, T. R., Blalock, A., Mason, M. F., and Williams, J. R., Jr. Relation of the Kidneys to Blood Pressure. Effects of Extracts of the Kidneys of Normal Dogs and of Dogs with Renal Hypertension on the Blood Pressure of Rats, *Arch. Int. Med.* **60**: 1058 (Dec.) 1937.

Williams, Harrison and Mason ⁸⁰ have obtained two different pressor substances from the extracts of kidneys. One of their extracts contains a pressor principle, which can be separated from fresh saline extracts of renal cortical tissue. This is precipitated by ammonium sulfate. The properties of this substance are similar to those of Tigerstedt's renin. The other pressor principle is obtained from the acetone-insoluble fraction of renal extract. Whether these two are identical or not is not known. The authors do not believe that the pressor effect of fresh saline renal extract is due to tyramine or like substances.

The work of Freeman and Page ⁸¹ is of particular importance. They found that complete sympathectomy in dogs did not prevent the development of hypertension from compression of the renal arteries. They conclude that hypertension produced in this manner is not mediated through increased peripheral resistance due to reflex sympathetic vasomotor action. There is no increase in the total volume of blood plasma, and it is not the result of a reflex increase in cardiac activity. They believe that the physiologic factors which normally control the level of arterial blood pressure are not etiologically concerned in the development of hypertension induced by compression of the renal arteries in dogs.

Page and Sweet ⁸² have studied the effects of hypophysectomy on the arterial blood pressure of dogs with experimental hypertension. They found that when hypophysectomy was done on animals in which hypertension had been induced and maintained for several months, the blood pressure fell to levels slightly above normal within a period of twenty days. Hypophysectomy in normal dogs resulted in only a slight reduction of pressure. If the constriction of the renal arteries was increased after hypophysectomy there was again a rise in blood pressure which varied somewhat with the general condition of the animals. With administration of thyroid to such animals after the blood pressure had been reduced by hypophysectomy, the blood pressure was again raised moderately. The injection of estrogenic substance (estrone, or theelin) and gonadotropic substance from the urine of pregnant women (antuitrin S) had no effect. It seems possible, as they believe, that this effect is an indirect one. It may be due to the lack of secretions of the

80 Williams, J. R., Harrison, T. R., and Mason, M. F. Observations on Two Different Pressor Substances Obtained from Extracts of Renal Tissue, *Am J M Sc* **195** 339, 1938.

81 Freeman, N. E., and Page, I. H. Hypertension Produced by Constriction of the Renal Artery-Sympathectomized Dogs, *Am Heart J* **14** 405, 1937.

82 Page, I. H., and Sweet, J. E. The Effect of Hypophysectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, *Am J Physiol* **120** 238, 1937.

adrenal and thyroid glands because of the absence of stimulation of these structures by the withdrawal of the hormones of the hypophysis

Glenn and Lasker⁸³ performed total thyroidectomy on dogs both before and after the induction of hypertension by constriction of the renal arteries. There was no alteration in the production and maintenance of the elevated blood pressure in either group of animals.

It is interesting to note that Jores⁸⁴ has obtained substances from serum extracts of patients with hypertension which caused an increase in the size of the adrenal cortex of mice. This substance was found in 6 cases of essential hypertension but was not present in patients with eclampsia or toxemia of pregnancy.

Oppenheimer and Prinzmetal⁸⁵ studied the brachial-digital pressure gradient in normal and hypertensive subjects and in their patient with adrenal pheochromocytoma. The average pressure gradient for patients with hypertension was found to be approximately the same as that found in persons with normal or low blood pressure. In 3 cases of extreme hypertension there was a notable reduction. Only in the patient with chronic pheochromocytoma was the pressure gradient markedly increased, indicating constriction of arteries larger than the digital arteries. They conclude that in hypertension there is no increased resistance offered to the flow of blood by arteries as large as the digital. This is in agreement with the observation of Perlow,⁸⁶ who states that arterial spasticity is controlled by the autonomic nervous system and can be relieved by sympathetic ganglionectomy. Arteriolar spasticity, on the other hand, is controlled by some local nervous or chemical mechanism, the nature of which is unknown, and is not relieved by sympathetic ganglionectomy.

Arnott, Kellar and Matthew⁸⁷ have studied the hypertension that accompanies serum nephritis. They contend that the hypertension of acute diffuse renal disease depends on the integrity of the renal nerve supply and that it is probable that the mechanism is an autonomic vaso-

83 Glenn, F, and Lasker, E P. Effect of Total Thyroidectomy upon Production and Maintenance of Experimental Hypertension, *Proc Soc Exper Biol & Med* **38** 158, 1938

84 Jores, A. The Role of the Hypophysis in High Blood Pressure, Especially in Essential Hypertension, *Klin Wchnschr* **15** 841, 1936

85 Oppenheimer, E T, and Prinzmetal, M. Role of the Arteries in the Peripheral Resistance of Hypertension and Related States, *Arch Int Med* **60**: 772 (Nov) 1937

86 Perlow, S. Differentiation Between Peripheral Arterial and Arteriolar Spasticity in the Selection of Cases for Sympathetic Ganglionectomy, *Surg, Gynec & Obst* **64** 1015, 1937

87 Arnott, W M, Kellar, R J, and Matthew, G D. Hypertension Associated with Experimental Serum Nephritis, *Edinburgh M J* **44** 205, 1937

constrictor reflex originating in the damaged kidneys. They doubt the possibility of a chemical mechanism which depends for its operation on the renal nerve supply.

Prohaska, Harms and Dragstedt⁸⁸ induced hypertension in normal dogs for periods as long as two weeks by the continuous intravenous injection of epinephrine hydrochloride. The amount necessary to maintain hypertension was sufficient to cause death from other systemic effects of this substance. They conclude that it does not seem probable that persistent hypertension in man can be due to hyperadrenalemia.

Binger and Craig⁸⁹ have reported an interesting case of sympathicoblastoma of the adrenal gland. The patient had persistent hypertension resembling the usual severe type of vascular hypertension without paroxysmal rises in pressure. Extensive sympathectomy was performed, with little fall in blood pressure. After exploration and removal of the tumor the blood pressure returned to normal and has remained so. It is interesting to note that this patient's basal metabolic rate was 61 per cent above normal.

Wolheim⁹⁰ has obtained from normal urine, urine from patients with chronic nephritis and urine of pregnant women a substance which is thermostable and has a definite depressor action. It was not obtainable from patients with hypertension. The intramuscular injection of this substance into patients with hypertension resulted in a definite fall in both systolic and diastolic pressure. The writer suggests that the absence of this substance may be responsible for hypertension.

Because of the conflicting findings reported after extensive sympathectomy, no attempt at this time will be made to discuss the physiologic influence of this operation.

Vaughan and Sullivan⁹¹ discuss the possibility of an allergic factor in essential hypertension. They cite the case of a patient who exhibited allergic reactions to a number of foods. Dietary restrictions resulted in the disappearance of the high peaks of pressure. Both the systolic and the diastolic pressure failed to return entirely to normal. The pressure was further reduced by limitation of mental and physical activities. Two other patients with food allergy responded with a rise in

88 Prohaska, J. V., Harms, H. P., and Dragstedt, L. R. Epinephrine Hypertension, *Ann Surg* **106** 857, 1937.

89 Binger, M. W., and Craig, W. M. An Atypical Case of Hypertension with a Tumor of the Adrenal Gland, *Proc Staff Meet, Mayo Clin* **13** 17, 1938.

90 Wolheim, E. A New Depressor Substance Elaborated by the Body and Its Meaning for Essential Hypertension, *Acta med Scandinav* **91** 1, 1937.

91 Vaughan, W. T., and Sullivan, C. J. On the Possibility of an Allergic Factor in Essential Hypertension, *J Allergy* **8** 573, 1937.

systolic and diastolic pressures after the ingestion of food to which they were known to be reactive Liston⁹² has had a similar experience He reports sharp falls in blood pressure after the removal of foods from the dietary of persons who exhibited sensitization to them

The susceptibility of the Negro to vascular disease has been spoken of for many years Weiss and Prusmack⁹³ have made comparative studies in regard to essential hypertension in a large group of Negroes and white persons The disease occurred a decade earlier in the Negro than in the white persons Of the Negroes, 10.1 per cent were below the age of 40, while only 3.6 per cent of the whites showed the early appearance of hypertension The sex distribution was about equal One or more of the major complications of hypertension occurred in more than 75 per cent of the Negroes, in contrast to a 66 per cent occurrence in white persons The mortality and morbidity of essential hypertension were found by Moritz and Oldt⁹⁴ to be greater in Negroes than in white persons The average age at the time of death was likewise lower for the Negroes

Guild, Kindell and Gibson⁹⁵ report 2 cases of extensive arteriolar sclerosis in 9 year old children with positive autopsy observations In 1 case there was complicating pyelonephritis There were extreme hypertension and marked cardiac hypertrophy in both but no evidence of myocardial failure The presence of malignant hypertension so early in childhood is worthy of note They have found in the literature reports of 20 other probable cases

Moritz and Oldt⁹⁴ have made an important study of the occurrence of arteriolar sclerosis in hypertensive and nonhypertensive persons They found that no type of chronic arteriolar disease was by itself pathognomonic of hypertension Every type was found in persons known to have a normal blood pressure The two most prominent and frequent types of arteriolar disease were found to be intimal hyalinization and intimal hyperplasia Both are regarded as primary pathologic processes The former is an aging phenomenon and is the counterpart in the arterioles of sclerosis in the arteries The second may be the result of nonexudative, productive arteriolitis They believe medial hypertrophy to be a secondary phenomenon due to distention of the vessels Medial degeneration may be in part primary or perhaps asso-

92 Liston, O Hypertension Caused by Food Allergy, *J Missouri M A*, **34** 199, 1937

93 Weiss, M M, and Prusmack, J J Essential Hypertension in the Negro, *Am J M Sc* **195** 510, 1938

94 Moritz, A R, and Oldt, M R Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am J Path* **13** 679, 1937

95 Guild, H G, Kindell, F B, and Gibson, T Arteriosclerosis in Childhood, *Bull Johns Hopkins Hosp* **62** 159, 1938

ciated with medial hypertrophy. While disease of the media may occur in persons without hypertension, severe types of medial disease were seen only in persons with chronic hypertension. Perhaps the most significant finding in the work of these observers is the fact that arteriolar disease of the kidneys was almost invariably associated with hypertension. It was present in 109 of the 200 cases studied, and 97 of these proved to be cases of chronic hypertension. The absence of arteriolar sclerosis in the kidneys, conversely, indicated the absence of hypertension. No comparable correlation was found with respect to any other organ or tissue. They conclude that the only significant site of arteriolar sclerosis concerned with the etiology of hypertension is in the kidneys. They have also observed that the most important factor determining the rate of progression of the disease, with early death from renal insufficiency, is dependent not on the degree of hypertension but on the progressive character of the renal arteriolar disease, with a more rapid rate of destruction of renal tissue. These observations can be correlated with those in experimental hypertension.

Rytand⁹⁶ has been able to produce hypertension in rats by partial occlusion of the aorta. This occurs only if there is living renal tissue distal to the occlusion. His findings in this respect are similar to those of Goldblatt. The mechanical obstruction due to stenosis of the aorta never resulted in hypertension when all the renal tissue was above the point of occlusion.

TREATMENT

During the past year few original ideas concerning the treatment of peripheral vascular disease have come to our attention. The majority of the published articles verify established methods or describe various modifications.

Silbert,⁹⁷ in a timely paper, discusses the evaluation of results in the treatment of peripheral vascular disease. He describes the improvement in circulation following occlusion of a major artery without any form of treatment. After occlusion occurs, collateral circulation develops quickly for about a year and continues to do so at a slower rate for at least two or three years longer. After this first period the circulation remains at a remarkably stationary level for an indefinite number of years, during which the collateral circulation is maintained. In patients with arteriosclerosis there follows a third period, in which the collateral circulation itself becomes involved in the arteriosclerotic process, and a progressive diminution of circulation results. In the

96 Rytand, D. A. Pathogenesis of Arterial Hypertension in Coarctation of the Aorta, *Proc Soc Exper Biol & Med* **38** 10, 1938.

97 Silbert, S. Evaluation of Results in Treatment of Peripheral Circulatory Diseases, *Am Heart J* **15** 265, 1938.

first period, treatment may accelerate the development of the collateral circulation, but it will develop without it. It is obvious that one must know to what stage the disease process has developed in order to evaluate therapy properly.

Silbert also considers the role of tobacco in the evaluation of therapy. Because of its vasoconstricting effect, tobacco alone may produce marked circulatory insufficiency in cases of partial organic occlusion. Hence, cessation of the use of tobacco will, in a number of cases, produce spontaneous improvement. Environmental changes in temperature and in the emotional state of the patient will likewise influence the size of the peripheral vessels and must also be considered in the proper evaluation of treatment.

Bernheim and London⁵⁰ report gratifying results in the treatment of arteriosclerosis by following a regimen somewhat similar to that employed for thromboangitis obliterans. It is their experience that vasospasm is an underlying process in both diseases. The rationale of their therapy was, therefore, to increase the blood supply to the extremity by, first, relieving the vasospasm and, second, by decreasing the viscosity of the blood. The latter results in an easier passage of blood through the narrow and rigid vessels. In order to relieve the vasospasm the use of tobacco was forbidden. Patients were warned against undue physical exertion, exposure to cold and emotional disturbances. A diet high in calcium and vitamins was prescribed because of its favorable influence on vasospasm. Sodium citrate, in doses of 250 cc of a 2 per cent solution, was given intravenously to lessen the viscosity of the blood. After this regimen the authors observed improvement in 83.9 per cent of the 99 cases of arteriosclerosis. In 79.6 per cent of the 54 cases of thromboangitis obliterans, improvement was also noted.

Sandstead and Beams⁹⁸ report the relief of pain of neurocirculatory origin in 13 diabetic patients by the oral administration of sodium chloride. In 10 cases the pain was of neuritic origin, and in 3 it was of arteriosclerotic origin. In the latter cases the histamine test was used as an index of circulatory improvement. The daily dosage was 0.25 to 0.5 Gm per kilogram of body weight given at interrupted intervals of two to four weeks over periods ranging from one to twelve months.

Favorable results in the treatment of endarteritis obliterans and ulcers were obtained by Teitge⁹⁹ with estrogen. Mild circulatory distur-

98 Sandstead, H. R., and Beams, A. J. Relief of Diabetic Pain of Neurocirculatory Origin by Oral Administration of Sodium Chloride, *Arch Int Med* 61:371 (March) 1938.

99 Teitge, H. Die Behandlung der Endangitis obliterans und des Ulcus cruris mit Sexualhormon, *Med Klin* 33:1153, 1937.

bances, such as coldness and tingling of the fingers, responded readily. Patients with decubitus ulcers, Raynaud's disease or diabetic gangrene did not respond favorably. Since endocrine disturbances were more common in elderly patients of either sex, he found this form of therapy most favorable in this group.

Kling and Sashin¹⁰⁰ used histamine iontophoresis in a large group of cases of Raynaud's disease, acroparesthesia, angioneurotic edema and thromboangitis obliterans. Relief from pain was obtained in 60 per cent of his cases. Solution of histamine prepared in a dilution of 1:2,000 was found to be most beneficial. He considers histamine superior to mecholyl (acetylbetamethylcholine chloride) because it has more effect on the arterioles and capillaries, with fewer systemic reactions. Murphy,¹⁰¹ using mecholyl iontophoresis, noted definite improvement in 31 of his 33 cases of thrombophlebitis. Edema subsided, and the patient was able to be up and about without the aid of a supporting bandage.

Edwards,⁶⁰ in his observations on phlebitis, stresses the influence of this disturbance on the sympathetic fibers of the extremity involved and its resulting vasospasm. To combat this he found heat, foreign protein or typhoid vaccine given intravenously, most efficacious. He believes that prolonged rest in bed is unnecessary, since the fearful stagnation clot seldom adheres to the walls of the veins, regardless of rest. It is his practice to tie off the deep vein in all cases in which an embolus had been dislodged, in order to prevent recurrence. Muller¹⁰² is also of the opinion that prolonged rest in bed is unnecessary and that the patient should be up, with a compression bandage on the involved extremity.

Numerous articles have been recently published concerning the therapeutic value of roentgen treatment of peripheral vascular disease. Cottenot¹⁰³ reports beneficial results in the treatment of endarteritis obliterans and vasomotor disturbances. He found it to be both safe and effective. Henschen and Becker,¹⁰⁴ reporting their results in acute,

100 Kling, D. H., and Sashin, D. Histamine Iontophoresis in Rheumatic Conditions and Deficiencies of Peripheral Circulation, *Arch Phys Therapy* **18** 333, 1937.

101 Murphy, H. L. The Treatment of Thrombophlebitis, *Surg, Gynec & Obst* **65** 100, 1937.

102 Muller, A. Die Thrombophlebitis und ihre Behandlung mit komprimierendem Gehverband, *Med Klin* **33** 793, 1937.

103 Cottenot, P. Zur Rontgenbehandlung der Endarteritis obliterans, *Strahlentherapie* **56** 569, 1936.

104 Henschen, C., and Becker, F. Rontgenbestrahlung der akuten, der subakuten und der chronischen Phlebitis und Thrombophlebitis, *Schweiz med Wchnschr* **67** 438, 1937.

subacute and chronic phlebitis and thrombophlebitis, found that four to twelve radiation treatments effected the disappearance of phlebitic symptoms. Each irradiation consisted of 100 to 200 roentgens, and the more severe the inflammatory process, the weaker the dosage. He believes that irradiation produces a general action by increasing the bactericidal action of the blood and stimulating the reticuloendothelial system and the formation of antibodies. Locally it produces alkalosis, dilatation of the capillaries, an increase in the lymphatic circulation and a reduction of edema and pain. Friedlander and Sgalitzer¹⁰⁵ obtained good results in migratory phlebitis by irradiating the spleen. They gave six doses of 150 roentgens each, two of which were given anteriorly, two posteriorly and the remaining two from the left side. The rationale of this type of therapy depends on the effect of the rays on toxins present in the reticuloendothelial system of the spleen.

The center of interest in peripheral vascular disease during the past year has been intermittent venous occlusion. The preliminary reports by Collens and Wilensky were reviewed last year, the details of this type of therapy and a résumé of the results obtained in a small group of cases being given. Recently they¹⁰⁶ have reported their experience in 124 cases. In addition to the technic previously described, an attempt was made to alleviate vasospasm by raising the environmental temperature. This was accomplished by simultaneously heating the extremity with short wave irradiation or diathermy. Best results were obtained in cases of thromboangitis obliterans and peripheral sclerosis in non-diabetic patients. In the former group ulcers or gangrene healed in 71 per cent of the cases, and rest pain was relieved within forty-eight hours in 85 per cent. In the latter group ulcers were healed in all cases and gangrene in 25 per cent of the cases. Complete relief from pain was obtained within forty-eight hours in 82 per cent, and in many the oscillometric readings increased. In cases of peripheral sclerosis with diabetes, relief from pain was noted in 60 per cent, and ulcers or gangrene healed in 62 per cent. In this group, amputation was required in 24 per cent of the cases while the patient was under treatment. All 7 patients with embolus and acute arterial thrombosis were relieved of pain, and 4 completely recovered. Seven patients with large chronic varicose ulcers responded favorably. The authors feel that this method is capable of "increasing vascular capacity as is evidenced by the following phenomena: relief of rest pain, increase in walking capacity,

105 Friedlander, E., and Sgalitzer, M. Die Phlebitis migrans und ihre Behandlung, *Med. Klin.* **34** 223, 1938.

106 Collens, W. S., and Wilensky, N. D. Intermittent Venous Occlusion in Treatment of Peripheral Vascular Disease, *J. A. M. A.* **109** 2125 (Dec. 25) 1937.

regeneration of tissues, improvement in the nutrition of nails, and the growth of hair over areas which had become denuded as the result of obliterative arterial disease”

Allen and McKechnie,¹⁰⁷ using a sphygmomanometric cuff above or below the knee, thus producing intermittent venous occlusion, were not able to produce any evidence of significant or consistent vasodilatation, as measured by the cutaneous temperature. Under basal conditions they studied a group of 19 patients with or without peripheral vascular disturbances. The fact that the final temperature of the skin in individual cases did not vary within a degree either above or below the original level was significant to them, in that vasodilatation did not take place. The Council on Physical Therapy,¹⁰⁸ however, in a preliminary report, states that tests indicate that both the cutaneous temperature and the oscillometric curves increase after the application of the Collens-Wilensky apparatus. It was also noted that during venous occlusion there was a filling and stretching of the venocapillary bed and during release reactive hyperemia took place which brought on vasodilatation. It was noted, however, that no provision is made in this type of treatment for emptying the vascular bed effectively, and for this reason a certain amount of continuous venous stasis exists. Kramer,¹⁰⁹ de Takáts, Hick and Coulter¹¹⁰ are in agreement with this report. Kramer in a study of 30 cases confirms the work of Collens and Wilensky. In 66.6 per cent of the cases definite benefit was obtained. Cramps were relieved in 77.7 per cent, fatigue in 83.3 per cent and pain in only 56 per cent, a figure considerably below that given by Collens and Wilensky. Although Kramer was unable to make complete studies, he did find an average increase in cutaneous temperature of from 1 to 3 C, as well as an increase in the oscillometric readings.

De Takáts, Hick and Coulter¹¹⁰ adopted a triphasic cycle, consisting of (1) elevation of the leg, (2) venous compression while the leg is still elevated and (3) lowering of the leg to a horizontal position, followed by release of the compression. Venous hyperemia was obtained by the use of an ordinary sphygmomanometer, the cuff of which was

107 Allen, E. V., and McKechnie, R. E. Effect of Intermittent Venous Occlusion on the Circulation of the Extremities, *J. Lab. & Clin. Med.* **22** 1260, 1937.

108 Collens-Wilensky Intermittent Venous Occlusion Apparatus. Preliminary Report, report of Council on Physical Therapy, *J. A. M. A.* **109** 131 (July 10) 1937.

109 Kramer, D. W. Periodic or Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease, *M. Rec.* **147** 99, 1938.

110 de Takáts, G., Hick, F. K., and Coulter, J. S. Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease, *J. A. M. A.* **108** 1951 (June 5) 1937.

8 inches (20 cm) wide. They were able to show that intermittent venous hyperemia in a normal person increased the oscillometric readings during the venous constriction, with further increase immediately after release. The systolic and diastolic blood pressures during the period of constriction remained unchanged but decreased immediately after release of the constrictor. When vessel spasm was released either by placing the extremities under a heat cradle or by sympathectomy, the results were similar. Less striking findings were obtained in patients suffering from arterial disease. A rest period after compression was advocated in order to prevent a refractory stage. The passive elevation of the extremity allowed the venocapillary bed to empty sufficiently. The necessity for the two last-mentioned procedures was demonstrated by measuring the oxygen content and saturation of the blood from the femoral vein draining the treated extremity. Oxygen saturation was found to be fairly well maintained. These authors conclude that the mechanism involved is a mechanical filling and stretching of the vascular tree because of compression. After release a chemical vasodilatation takes place as a result of an oxygen debt, thus affecting the capillary pressure, the lymph flow and the saturation of the tissues and venous blood with oxygen.

The practical aspect of their study resulted in a simple, inexpensive method of producing intermittent venous hyperemia by utilizing the aforementioned triphasic cycle. A sphygmomanometer with an 8 inch cuff is inflated by the patient or an attendant. The amount of pressure varies between 60 and 90 mm of mercury, never exceeding the diastolic pressure. In cases of edema, cyanosis, ulceration or gangrene, 40 mm of mercury is considered maximum at the beginning. The duration of compression depends on the appearance of definite rubor, usually within one or two minutes. The duration of release always exceeds the period of compression, usually being twice as long. During the rest period, one minute is always allowed for elevation. Treatments are given twice daily for periods of thirty minutes. Ten cases of obliterative vascular disease were studied. Improvement in coldness and numbness was noted in 5 patients, 7 patients were able to walk farther before claudication developed and rest pain was relieved in 4 patients.

Recently, de Takáts¹¹¹ reported his observations on 50 patients who had had fifty treatments or more. He noted that coldness and numbness were the first symptoms to be relieved. Intermittent claudication improved slowly. Rest pain was the last to be relieved. This he explains by the fact that rest pain is a sign of serious circulatory damage.

¹¹¹ de Takáts, G. Intermittent Venous Hyperemia for the Treatment of Peripheral Vascular Disease, *Physiotherapy Rev* 18 7, 1938

and is found in persons with little ability to form a collateral circulation. Pure vasospastic circulatory disorders were not influenced. If the pressure in the cuff is lowered, this form of therapy can be used on patients with chronic edema, lymph stasis or chronic ulcerations. Phlebitis, lymphangitis and spreading infections are listed as contraindications to this form of therapy.

Confirmatory reports are also made by Brown and Arnott,¹¹² who limited their study to cases of obliterative vascular disease. Thirteen cases are reported, and good results were noted in all except 1 case. Nocturnal pain was invariably relieved, in some instances within a few hours after treatment was started. Intermittent claudication, present in 10 of the cases, was relieved in all except 2. Six of the patients had varying amounts of gangrene, and healing was promoted in all except 1. The same authors,¹¹³ in a preliminary report, describe three new types of apparatus for use in the intermittent filling of the cuff. Two of these machines are electric air pumps, while the other is a water pump. Wilson and Ogston¹¹⁴ describe clearly a novel apparatus for intermittent venous occlusion, utilizing water pressure and siphonage to obtain desired pressure and release in the cuff. Using this apparatus they obtained good results in 10 patients suffering from claudication and gangrene. In this series the rest period was lengthened to four minutes.

Articles continue to be published confirming, standardizing and modifying suction-pressure therapy in peripheral vascular disease. Veal¹¹⁵ advocates the visualization of the peripheral vessels by means of thorium dioxide in order to prognosticate the possible value of this form of therapy. He noted that in patients with an extensive collateral circulation the best results were obtained. In patients with marked diminution of the vascular bed, improvement was only slight, while in those with high occlusion and extensive vascular damage no improvement was ever noted. A small group of patients are reported to substantiate his contentions. Studies on the oxygen saturation of venous blood from the popliteal and superficial veins showed that in the first group it increased after one hour of therapy, while in those with little collateral circulation the saturation remained unchanged.

112 Brown, J. J. M., and Arnott, W. M. Treatment of Obliterative Vascular Disease by Intermittent Venous Occlusion, *Brit. M. J.* **1**: 616, 1938.

113 Brown, J. J. M., and Arnott, W. M. Intermittent Venous Occlusion in the Treatment of Obliterative Vascular Disease, *Brit. M. J.* **1**: 1106, 1937.

114 Wilson, C., and Ogston, A. G. Treatment of Peripheral Vascular Disease by Intermittent Venous Occlusion, *Lancet* **1**: 606, 1938.

115 Veal, J. R. Alternate Suction and Pressure Therapy in Peripheral Obliterative Vascular Disease, *Arch. Phys. Therapy* **18**: 640, 1937.

Krock¹¹⁶ introduces a new, simplified suction-pressure machine of the light, compact, portable type in which the time ratio of suction to pressure can be changed to any desired amount. This machine is utilized particularly to obtain the ratio of one minute suction to one minute pressure, which has been found to be optimum, especially in cases of arteriosclerotic origin. He has noted that at the 1:1 ratio, anoxemia does not occur and in some instances the oxygen saturation of venous blood actually increases. He also reports a successful series of suction-pressure treatments of a patient with chronic obliterative arterial disease complicated by varicose veins. With the usual method, phlebitis readily developed, but after an elastic bandage was applied the treatments were carried out successfully. Yeager¹¹⁷ believes that suction-pressure therapy is inadequate in thromboangitis obliterans but beneficial in a large percentage of selected cases, particularly cases of arteriosclerotic peripheral vascular disturbances with fixed sclerosis of the arterioles. Leiner¹¹⁸ reports his results obtained in 26 patients suffering from severe vascular damage. In the majority of the patients treated, relief from pain was obtained whether they were ambulatory or not. Trophic ulcers and gangrene improved. Becker¹¹⁹ found this method of treatment satisfactory and advocates its use even though complications develop.

Eighty cases of occlusive arterial disease of various types in which suction-pressure therapy was used were studied by O'Neil¹²⁰. The best results were obtained in cases of frozen feet and arteriosclerosis of diabetic origin. Good results were obtained in about half the cases of arteriosclerosis of nondiabetic origin, thromboangitis obliterans and peripheral embolism. He emphasizes the fact that in peripheral occlusion due to emboli, good results cannot be expected from either embolectomy or suction-pressure if not carried out within four hours of the onset. It is his belief that suction-pressure therapy in the future will prove to be the procedure of choice. Rykert and Graham⁵⁸ are of a similar opinion, having had experience with both embolectomy and suction-pressure therapy. They believe that the final result of the treatment of embolic occlusion depends on the severity

116 Krock, F. H. A Simplified Apparatus for Pressure-Suction Therapy of Obliterative Arterial Disease of the Extremities, *South M. J.* **31** 294, 1938.

117 Yeager, G. H. Passive Vascular Exercise in Peripheral Vascular Disease, *Arch. Phys. Therapy* **19** 158, 1938.

118 Leiner, G. Die Saug-Druck-Behandlung der Erkrankungen der peripheren Gefäße, *Klin. Wchnschr.* **16** 783, 1937.

119 Becker, S. Erfahrungen mit der "Saug-Druck"-Behandlung peripheren Durchblutungsstörungen, *Med. Klin.* **33** 1132, 1937.

120 O'Neil, E. E. Suction-Pressure Therapy in Peripheral Vascular Disease, *New England J. Med.* **217** 828, 1937.

of the associated primary disease and that the results of suction-pressure therapy surpass those of embolectomy. They suggest that the ideal method of treatment for acute arterial occlusion is a combination of the nonoperative methods, namely, suction-pressure therapy, antispasmodic drugs and heat applied to the body.

SURGICAL TREATMENT A CRITICAL REVIEW

By DR. DE TAKATS AND DR. BECK

The surgical treatment of peripheral vascular disease is becoming more stabilized, new methods have not been described, but the more recent surgical procedures have been subjected to a closer scrutiny in regard to late results and the mechanism of their action. In this year's review we are including surgical procedures which are aimed at modifying the extracardiac part of the vascular tree and have not limited ourselves to operations on the vascular system of the extremity.

EMBOLECTOMY

Cornell¹²¹ reviews the literature on embolism, he locates the site of obstruction by the point of maximum tenderness, which, however, in our experience is misleading. He stresses the fact that embolectomy should be performed within the first twelve hours. Of 20 reports of cases collected from the records of the New York Hospital, none records successful embolectomy. Rykert and Graham⁵⁸ report on a series of 36 patients from the Toronto General Hospital. The authors feel that in embolism of the large peripheral arteries, two distinct types of pain may arise. There is, at the onset of the attack, pain of short duration but of maximum severity which is probably due to arterial spasm at the level of the occlusion. This pain merges into and is replaced by late pain of ischemic causation, which arises distal to the occlusion. In arterial thrombosis the early pain is absent. Attention is called to the frequency of spontaneous recovery of the circulation in acute embolic occlusion of the upper extremity. The authors believe that the ideal method of treatment for acute arterial occlusions is a combination of the nonoperative methods, namely, suction and pressure therapy, antispasmodic drugs and heat to the body. They have performed embolectomy in 11 cases, but their experience with this method has been unsatisfactory.

Lund¹²² reports 55 cases of peripheral embolism. In the 30 cases in which the arteries were operated on, there were 27 embolectomies,

121 Cornell, N. W. Arterial Embolism and Thrombosis, *S. Clin. North America* **18** 405, 1938.

122 Lund, C. C. Treatment of Embolism of the Greater Arteries, *Ann. Surg.* **106** 880, 1937.

2 explorations and 1 ligation. Of the 27 patients on whom embolectomy was performed, 12 died in the hospital (44 per cent), 5 had amputations and 10 obtained successful results (37 per cent). Of 30 patients with embolism which was treated conservatively, 24 died in the hospital (85 per cent), 3 were discharged with good circulation (8 per cent) and 3 had amputations. The author believes that embolism of the upper extremities rarely leads to gangrene and that embolectomy is not needed. Results without embolectomy when the lower extremities are involved are poor.

Recently the impression has gained ground that early conservative measures make embolectomy unnecessary. The answer to this problem can be found by examining the fate of limbs after embolectomy and after conservative measures. Five patients who had survived acute vascular occlusion without gangrene and without embolectomy were studied.⁵⁹ In each case the extremity was pulseless and atrophic, the muscles were contracted and fibrosed and the skin was scaly and mottled. The legs were painful because of ischemic neuritis, and severe intermittent claudication was present. Such limbs cannot be compared with those from which a clot has been successfully extracted. For this reason we feel that in the small group of cases in which early conservative measures have not brought about an improvement in circulation but in which the limb is not yet ready for amputation, embolectomy should be attempted. Most frequently the groin and the popliteal fossa are explored, local anesthesia being induced. Clots in the aorta and in the common iliac artery may be approached from an incision in the groin and brought down by subperitoneal massage, as suggested by Nystrom.

PROXIMAL LIGATION OF THROMBOSED VEINS

In cases of deep thrombophlebitis of the lower extremities or pelvis in which fever persists for many weeks and months, the leukocyte count remains high and anemia develops or in which one or two showers of pulmonary embolism have occurred, ligation of the iliac vein above the thrombosis seems justifiable.¹²³ In weighing the results of such a ligation it must be remembered that the venous obstruction is already present and that the additional ligation will not add to the embarrassment of venous return if important tributaries are avoided. The drop in septic temperature and the cessation of further showers of pulmonary embolism were gratifying, according to both reports.¹²³

¹²³ Bancroft, F. W. Proximal Ligation and Excision of Veins for Septic Phlebitis, *Ann Surg* **106** 308, 1937. Neuhof, H. Excision of Vein for Suppurative Thrombophlebitis, *ibid* **106** 311, 1937.

ARTERIOVENOUS ANEURYSM

An important contribution to this subject, which no one should miss who wishes to gain an insight into congenital and acquired communications between the arterial and the venous system, is the monograph by Holman¹²⁴ This treatise is the result of painstaking experimental research and clinical observations which have been conducted for many years The experimental arteriovenous fistula is described, with its physiologic effects on the heart, the blood pressure, the concentration of the blood and the total volume of blood Clinical observations on acquired arteriovenous communications follow There are chapters on intracranial, intrathoracic and mycotic arteriovenous fistulas and a description of congenital arteriovenous aneurysms Of greatest interest to internists are the observations on ductus arteriosus and intracardiac fistulas, with some hopeful surgical implications Interesting protocols are available in the appendix, and a complete bibliography is supplied

The author assigns to the center of interest the variations of the total blood volume and its control in the body He believes that valvular defects, abnormal congenital openings, aortic insufficiency, pulmonary insufficiency, a patent ductus and interventricular defects all produce a mechanical inefficiency which at their inception shows a lowered blood pressure which is corrected by an increase in blood volume Future investigations, with perhaps improved methods, will have to confirm this interesting conception

In a patient suffering from a pea-sized aneurysm of the circle of Willis, Dandy¹²⁵ placed a silver clip on the neck of the sac, which promptly collapsed, and then seared it with the electric cautery All neurologic signs and symptoms, such as ptosis and shooting pain over the eye, disappeared This is the first attempt to cure an aneurysm at that location by a direct attack In the discussion of this paper, Rudolph Matas¹²⁶ gives a classic description of aneurysm of the circle of Willis, a small treatise in itself, to which we could not do justice in a short abstract He points out that while extracranial ligation of the internal or common carotid artery remains the safest method of approach for all the aneurysms of the sellar, parasellar and infrachnoid carotid tract, no curative effect can be expected in the case of an aneurysm that rises from the branches of the circle of Willis except by a direct attack

124 Holman, E Arteriovenous Aneurysm Abnormal Communications Between the Arterial and Venous Circulations, New York, The Macmillan Company, 1937

125 Dandy, W E Intracranial Aneurysm of the Internal Carotid Artery, *Ann Surg* **107** 654, 1938

126 Matas, R Aneurysms of the Circle of Willis, *Ann Surg* **107** 660, 1938

SCALENOTOMY

The syndrome producing pain of ulnar distribution and vascular spasms, with radiation to the neck, shoulder and precordial region, is discussed by Spurling and Bradford¹²⁷ In none of their cases was there any roentgenographic evidence of cervical rib In 17 of 20 cases perfect relief was obtained by complete section of the anterior scalenus muscle In 3 cases improvement but not complete cure was obtained The authors believe that some cases of birth palsy without Horner's syndrome may be due to this mechanism The scalenus syndrome may produce unilateral headache simulating migraine¹²⁸ or precordial pain simulating coronary disease¹²⁹

The incidence of cervical rib in 1,000 children under 13 years was 1.2 per cent¹³⁰ In only 3 of the 12 children were there symptoms such as pain in the neck and arms, torticollis and atrophy of the extremity Symptoms are not produced as a rule until ossification of the ribs takes place and until there is descent of the shoulder girdle

SYMPATHECTOMY

The anatomic features of the sympathetic outflow to the extremities are still under debate An important and timely contribution is that of Kuntz and his associates¹³¹ They point out that if preganglionic section, as advocated by Telford and by Smithwick and White (as cited in our last review), is carried out, important preganglionic connections between the cord and the inferior cervical ganglion are left intact, so that denervation is incomplete They conclude that preganglionic components of the first thoracic nerve do play a significant part in the sympathetic innervation of both the sweat glands and the vascular musculature of the upper extremities Thus complete sympathectomy of the arm cannot be accomplished by any operation which leaves the first thoracic nerve with its white ramus intact

This study is an anatomic confirmation of our clinical experience that preganglionic sympathectomy is incomplete and that recurrences are not less frequent than after the postganglionic method¹³²

127 Spurling, R. G., and Bradford, F. K. Scalenus Neurocirculatory Compression, *Ann Surg* **107** 708, 1938

128 Kleinberg, S., and Levine, M. A. Headache as Symptom of Cervical Rib, *Ann Surg* **105** 299, 1937

129 Reid, W. D. Pressure on the Brachial Plexus Causing Simulation of Coronary Disease, *J. A. M. A.* **110** 1724 (May 21) 1938

130 Davis, D. B., and King, J. C. Cervical Ribs in Early Life, *Proc Inst Med Chicago* **12** 88, 1938

131 Kuntz, A., Alexander, W. F., and Furcolo, C. L. Complete Sympathetic Denervation of the Upper Extremities, *Ann Surg* **107** 25, 1938

132 de Takáts, G. Analysis of End Results Following Sympathectomy for Peripheral Vascular Disease, *Am Heart J.*, to be published

An important anatomic description of the "ascending pelvic colonic nerves" is given by Trumble¹³³ In man the arrangement resembles that in herbivora He believes that the description given by Telford and Stopford is inaccurate For denervation of the lower extremity, the author simply cuts the chain at the upper border of the fourth lumbar vertebra and divides the gray ramus to the third lumbar nerve He believes that the results are practically the same as those obtained by extensive ramisection with division of the trunk

The effect of sympathectomy, previously studied in man, has been reinvestigated by the same methods in the dog by Freeman and Zeller¹³⁴ After removal of the vasomotor control, the circulation seems to be dependent on the metabolic requirements of the tissues This was found to be true in previous experiments on man, although the results were somewhat variable, in man the reflex secretion of epinephrine induced by unavoidable emotional disturbances could not be excluded In order to eliminate the adrenal factor, the experiments were repeated on dogs in which one adrenal gland had been removed and the other denervated It was found that the oxygen and carbon dioxide contents and the difference in p_H of the arterial and venous blood were constant in a single experiment over wide ranges of blood flow and metabolism The volume flow of blood through the paw varied directly with the temperature of the bath in which the paw was immersed

These findings add significant arguments for the hypothesis that the circulation after sympathectomy is controlled by the metabolic needs of the tissues but is no longer serving the purposes of heat regulation and is independent of external and internal stimuli that arrive to the vessels through the sympathetic fibers As emphasized elsewhere, this is an important argument for sympathectomy in peripheral vascular disease¹³⁵

The blood flow before and after sympathectomy was measured in dogs with a Reinstromuhr by Schneider¹³⁶ He found an increase of from 60 to 100 per cent immediately, several months, and as long as two years, after the operation Arteries both to the skin and to the muscles showed an increase in flow Stimuli from the carotid sinus

133 Trumble, H C Strategic Points in the Lumbar and Sacral Outflows of the Autonomic Nervous System Sympathetic Denervation of the Lower Limbs, *M J Australia* **2** 958, 1937

134 Freeman, N E, and Zeller, J W The Effect of Temperature on the Volume Flow of Blood Through the Sympathectomized Paw of the Dog with Observations on the Oxygen Content and Capacity, the Carbon-Dioxide Content, and the p_H of the Arterial and Venous Blood, *Am J Physiol* **120** 475, 1937

135 de Takats, G Sympathectomy in Peripheral Vascular Disease, *Arch Int Med* **60** 990 (Dec) 1937

136 Schneider, D Experimentelle Untersuchungen zur lumbalen Sympathektomie, *Beitr z klin Chir* **167**, 414, 1938

were ineffective. He found not only constrictors but dilators in the sympathetic chain and believes that he obtained evidence of afferent sensory impulses by stimulating the central end of the trunk.

The sympathetic vasodilator fibers are discussed in a critical review by Burn,¹³⁷ who has contributed so much to the subject. He emphasizes the variations in different animals and feels that if knowledge of the sympathetic control of blood vessels had been based on the hare and not the cat, the current teaching might be different. In the muscles of the dog cholinergic vasodilators are readily demonstrable but not in the skin except that of the ear. In the rabbit and the monkey there are a few, in the dog and in the hare there are many. In man previous work of Lewis and Pickering demonstrated their presence.

This review, we believe, is an excellent argument against a blind application of cat physiology to conditions in man.

The overawed clinician has been put in his place so often by the experimentalist that his only answer to many problems is clinical research, with its well recognized limitations.

As a measure of sympathetic activity or paralysis, Richter and Levine¹³⁸ advocate the measurement of the resistance of the skin to the galvanic current. Cervicothoracic sympathectomy in 10 patients consistently produced a large increase in electrical resistance of the skin of the palms and less increase in the backs of the hands. Lumbar sympathectomy affected the same change in the dorsal and plantar surfaces of the foot.

We have found this method useful in detecting incomplete sympathectomy, in which a strip of skin of ulnar or femoral distribution remains moist or maintains its low resistance.

Surgical procedures on the sympathetic nervous system are for relief of symptoms rather than for eradication of diseased structures, as pointed out by Lehman.¹³⁹ Almost all diseases produce symptoms through the activity of the autonomic nervous system, such as fever and vomiting. In some diseases, however, symptoms of autonomic imbalance predominate, as in Raynaud's disease, and their symptomatic treatment by surgical means is warranted.

The argument as to whether preganglionic section is preferable to postganglionic sympathectomy still continues. J. C. White,¹⁴⁰ in his survey of surgery of the sympathetic nervous system, restates that pre-

137 Burn, J. H. Sympathetic Vasodilator Fibers, *Physiol Rev* **18** 137, 1938.

138 Richter, C. P., and Levine, M. Sympathectomy in Man. Its Effect on the Electrical Resistance of the Skin, *Arch Neurol & Psychiat* **38** 756 (Oct) 1937.

139 Lehman, E. P. The Surgery of the Sympathetic Nervous System, *Surgery* **2** 426, 1937.

140 White, J. C. Progress in Surgery of the Autonomic Nervous System, *New England J Med* **217** 660, 1937.

ganglionic section for disorders of the upper extremities produces results which are comparable to the good results obtained by the customary lumbar sympathectomy for the lower extremities. After preganglionic section the vasoconstriction seen after the use of tobacco does not occur.

Telford¹⁴¹ reports on twenty-five preganglionic sympathectomies and is satisfied with the results. He believes that the usual cervicothoracic sympathectomy should not be done, regeneration is avoided by implanting the sympathetic chain into the scalenus anticus muscle. Fibers from the first white communicating ramus are left intact, but they go chiefly to the head and can be ignored as far as the upper extremity is concerned. This is not in accord with the studies of Kuntz and his co-workers. Curiously, another study on Telford's material, published by Simmons and Sheehan,¹⁴² presents the conclusion that a recurrence cannot be explained by Lewis' theory of the local fault in the vessel wall nor by the theory offered by White and Telford of sensitivity to epinephrine, which occurs a few days after operation, but that it is most probably due to an incomplete operation or to regeneration of fibers. They properly point out that the search for the cause of relapse of the Raynaud phenomenon following sympathectomy for the arm is one of the most important problems today in vascular surgery. Patients in whom block of the ulnar nerve fails to produce a rise in cutaneous temperature immediately after the operation may show such a rise later and have clinically a recurrence. The implantation of the cut end of the chain to prevent recurrence is reemphasized. Another group of patients show sweating immediately after the operation, this cannot be counted as a relapse but the result of an incomplete operation.

Observations in our clinic have prompted us to return to cervicothoracic ganglionectomy, although in a somewhat extended form, as after preganglionic section all the patients showed incomplete denervation and early clinical recurrence.

That regeneration is at least one definitely established reason for the recurrence of tonus is further corroborated by the excellent studies of Grimson, Wilson and Phemister,¹⁴³ who showed that after complete sympathectomy in the dog there occurred an initial drop in blood pressure, which returned to the preoperative level in about six months. They believe that during the period of lowered blood pressure the peripheral vascular tonus maintains the blood pressure but later there

141 Telford, E. D. S. Sympathetic Denervation of the Upper Extremity, *Lancet* **1** 70, 1938.

142 Simmons, H. T., and Sheehan, D. An Injury into "Relapse" Following Sympathectomy, *Lancet* **2** 788, 1937.

143 Grimson, K. S., Wilson, H., and Phemister, D. B. The Early and Remote Effects of Total and Partial Paravertebral Sympathectomy on Blood Pressure, *Ann Surg* **106** 801, 1937.

is a return of central control, even though this is not complete. When the central end of the sciatic nerve was stimulated or when the intracranial pressure was raised, the blood pressure rose, although a close study of the graphs indicates that the rise was incomplete. The authors suggest the possibility of the existence of vasomotor fibers in an extra-sympathetic pathway.

SPLANCHNIC NERVE SECTION

The report cited in the preceding paragraph justly causes one to consider the effect of partial sympathectomy on hypertension in human beings. Page and Heuer¹⁴⁴ report 9 cases of transthoracic splanchnic section, 6 of the patients had severe essential hypertension and 3 malignant hypertension. Of the 6 patients suffering from essential hypertension, all had relief from subjective symptoms, but in 3 these returned within a year. The blood pressure fell in all cases but reached the preoperative level within six months. Urea clearance and concentration-dilution tests seemed unaffected by the operation. The pressor response to cold was not consistently altered. Papilledema disappeared in 3 cases but reappeared within a few months. The authors feel that this type of operation did not result in sufficient improvement to encourage further trial.

In previous years these authors advocated extensive section of the anterior roots, which they seem to feel offers better end results. To us, section of the anterior roots seems far too mutilating for the benefits obtained.

From the pioneer group of workers on the surgical treatment of hypertension comes a study of the physiologic effects of extensive sympathectomy for essential hypertension. Adson¹⁴⁵ has abandoned anterior root section and partial resection of the adrenal glands and now removes the splanchnic nerves, part of the celiac ganglion and the two lumbar sympathetic ganglions in two stages. Operation is advised if after the administration of sedatives or vasodilators a sizable reduction of blood pressure, especially that of the diastolic pressure, is obtained. An age of over 50, congestive heart failure, angina pectoris, marked renal damage and advanced arteriosclerosis are regarded as contraindications, but patients with retinitis, an inverted T wave, albuminuria and cerebral accident with recovery or slight reduction in renal function have not been excluded. They have had no death in 108 cases. In the favorable cases the operation resulted in reduction of blood pressure, reversion of the T wave, diminished libido and marked

144 Page, I. H., and Heuer, G. J. Effect of Splanchnic Nerve Section on Patients Suffering from Hypertension, *Am J M Sc* **193** 820, 1937.

145 Allen, E. V., and Adson, A. W. Physiological Effects of Extensive Sympathectomy for Essential Hypertension, *Am Heart J* **14** 415, 1937.

improvement with regard to headaches, nervousness and precordial pain. Of 44 patients who could be followed, 20 showed no reduction in blood pressure, 13 a fair result and 11 an excellent result. Many patients have had amelioration of symptoms without a reduction of blood pressure. Allen and Adson feel that their results have been sufficiently encouraging to warrant further trial of the method.

Obviously the selection of cases constitutes at present one of the most important problems in the surgical treatment of hypertension. Davis and Barker¹⁴⁶ accept only such patients with essential hypertension as have been proved to resist cyanate therapy, are young and are free from renal damage and whose blood pressure shows marked fluctuations. They report on 6 patients. The immediate fall in blood pressure was restored within ten days in all cases. However, 2 patients who showed no response to cyanate therapy have become responsive to the drug. The authors have no explanation for this effect.

Our observations on splanchnic section for essential hypertension have led us to conclude (1) that the distinction between essential extra-renal hypertension and renal hypertension is not easily made, (2) that the urea clearance is the most sensitive test of renal function, but even this test may fail in early renal damage, (3) that restoration of blood pressure occurred in all cases within a few weeks to a few months, and (4) that subjective improvement is marked and cannot be gaged by readings of blood pressure. At present we are studying the mechanism which is responsible for the restoration of blood pressure and are watching for changes other than those in the blood pressure following the operation.

ADRENAL DENERVATION

In previous years the literature contained several favorable reports dealing with adrenal denervation for the treatment of essential hypertension. An anatomic study of Hollinshead and Finkelstein¹⁴⁷ indicates that after resection of the lower thoracic and upper lumbar sympathetic chain in cats, regeneration of the nerves took place, with corresponding changes in the adrenal glands, within three months. The regenerated fibers arose from the ganglions and were unmyelinated. They believe that in larger animals sufficiently long segments might be removed to prevent regeneration and that the scar tissue so formed might provide an effective barrier.

A sustained hypertension was produced in dogs for periods up to two weeks by the continuous intravenous infusion of epinephrine.

¹⁴⁶ Davis, L., and Barker, M. H. The Surgical Problem of Hypertension, *Ann Surg* **107** 899, 1938.

¹⁴⁷ Hollinshead, W. H., and Finkelstein, H. Regeneration of Nerves to the Adrenal Gland, *J Comp Neurol* **67** 215, 1937.

hydrochloride by Dragstedt and his co-workers⁸⁸ The amount required, however, was sufficient to cause death from the other systemic effects of the hormone, of which the inhibition of the motility of the gastrointestinal tract and the derangement of carbohydrate metabolism were probably the most important For this reason it does not seem probable that persistent hypertension in man is due to hyperadrenalemia

Rogoff and Marcus¹⁴⁸ have accumulated experimental evidence that the amount of epinephrine in circulation which is capable of causing sustained elevation of blood pressure would produce effects other than hypertension and would not be tolerated for more than a relatively short period Besides, epinephrine disappears from the blood rapidly They have also demonstrated that an increased concentration of epinephrine in the systemic circulation does not produce a detectable increase in epinephrine secretion from the adrenal glands They deprecate the clinical practice of intervention on the adrenal glands as a treatment for hypertension

In analyzing these experimental findings from the clinical standpoint, one must be impressed with the clearcut evidence that increased epinephrine secretion is not a cause of hypertension in human beings This by no means excludes the possibility that certain substances which are produced in ischemic kidneys could not sensitize blood vessels to the action of epinephrine In such a sense, then, the diminution in the output of epinephrine would still exert some influence on hypertension

CELIAC GANGLIONECTOMY

Crile,¹⁴⁹ who has now performed a total of 391 operations on the sympatheticoadrenal system in 231 cases, first advocated adrenal excision, then adrenal denervation and later splanchnic section, finally, he has done 239 celiac ganglionectomies on 144 patients The subjective symptoms, such as headaches, nervousness, dizziness, fatigue, palpitation and irritability, have been relieved over a period of a year in 78 per cent of the cases Even though the blood pressure has not returned to normal in a number of cases, the subjective improvement has been marked Moreover, these patients tend to become calmer and more equable in temperament, and the violent uprushes of blood pressure, with the disastrous results, which may accompany emotional outbursts may be mitigated

Obviously this operation is just an extensive splanchnic nerve section with adrenal denervation It more effectively prevents regeneration by eliminating a large group of cell stations in the celiac ganglions

148 Rogoff, J. M., and Marcus, E. Supposed Role of the Adrenals in Hypertension, *J. A. M. A.* **110** 2127 (June 25) 1938

149 Crile, G. The Clinical Results of Celiac Ganglionectomy in the Treatment of Essential Hypertension, *Ann. Surg.* **107** 909 (June) 1938

That such patients become calm, are less excited, put on weight and have a definite change in personality has also been our impression of diabetic and hypertensive patients who have been subjected to splanchnic nerve section. As untoward effects on metabolism, intestinal motility and other functions are not observed, it seems to us that if any intervention on the sympathetic nervous system is considered at all, celiac ganglionectomy is the method of choice.

AMPUTATIONS

Arnell¹⁵⁰ reports on 117 patients with diabetic gangrene from the Maria Hospital in Stockholm seen between 1917 and 1934. There were 45 women to 72 men, 28 per cent were treated conservatively, 22 per cent had minor amputations and 50 per cent had major amputations. All major amputations were done above the knee. The total mortality was 27.4 per cent, for the amputations, 38 per cent. Causes of death in the order of their frequency were coronary thrombosis, sepsis, pulmonary embolism and pneumonia. Fifty per cent of all surviving patients were dead within a short time after dismissal from the institution.

Meleney¹⁵¹ finds that hemolytic streptococci and staphylococci, and gas gangrene and tetanus organisms, as well as microaerophilic streptococci, are the organisms to be feared in amputations. If the gangrene is sharply demarcated, there is less danger of spreading infection than when there is much necrobiotic tissue in the process of breaking down. Material for culture should be taken from the muscles and the lymphatic system, if there is any doubt of infection, it is better to leave the stump open and treat it with a suspension of zinc peroxide.

Callander¹⁵² reports on further experience with his method described in 1936.¹⁵³ In the 80 cases reported, the age in most of which was over 65, the mortality rate was 13 per cent, with only 1 case of post-operative gas gangrene.

Beverly Smith¹⁵⁴ states that the mortality in 50 amputations through the thigh for diabetic gangrene was 45 per cent. By the method suggested by him (which was described in a previous review¹⁵³), it dropped

150 Arnell, O. De la gangrene diabetique, *Acta chir Scandinav* **80** 464, 1937.

151 Meleney, F. L. Bacteriology of Amputations, *S Clin North America* **18** 321, 1938.

152 Callander, C. L. "Tendoplastic" Amputation Through the Femur at the Knee. Further Studies, *J A M A* **110** 113 (Jan 8) 1938.

153 Scupham, G. W., and de Takats, G. Peripheral Vascular Diseases. Review of Some of the Recent Literature and Critical Review of Surgical Treatment, *Arch Int Med* **58** 531 (Sept) 1936.

154 Smith, B. C. The Therapy of Surgical Complications of Diabetes Mellitus at Presbyterian Hospital in New York City, 1930-1935, *Surgery* **2** 509, 1937.

to 18.1 per cent in 20 cases. When the lesion was infected, sulfanilamide applied locally seemed helpful. In arteriosclerotic gangrene, Smith¹⁵⁵ again emphasizes the advantages of his plastic amputation through the lower portion of the leg, which facilitates the wearing of an artificial limb.

Silbert¹⁵⁶ treats all patients suffering from thromboangitis obliterans with 5 per cent salt solution, ulcers are treated with cod liver oil. If marked pain is present and limited to the foot, crushing of the sensory nerves often gives relief for six months or a year. Up to 1925 at least one extremity was amputated in 60 per cent of the cases. Since 1925 only 6.4 per cent of 619 patients have required amputation, but only 2.7 per cent of those who truly cooperated have required amputation. The most important factor in obtaining results is complete abstinence from tobacco. If amputation is inevitable, an effort should be made to save the knee joint, as this will greatly facilitate the rehabilitation of the patient.

We have made considerable use of the Callander and the Smith type of amputation and believe that these methods deserve wider recognition. Both the preparation of the patient and the observation of technical details can reasonably reduce the mortality. The unavoidable mortality, due mainly to involvement of the cardiovascular apparatus, will always vitiate the late results.

155 Smith, B. C. Amputation for Arteriosclerotic Gangrene, *S. Clin. North America* **18** 357, 1938.

156 Silbert, S. Amputations in Thromboangitis Obliterans, *S. Clin. North America* **18** 359, 1938.

News and Comment

American Board of Internal Medicine, Inc—Written examinations for certification by the American Board of Internal Medicine will be held in various parts of the United States on Monday, Oct 17, 1938, and on Monday, Feb 20, 1939

A formal application must be received by the secretary before September 15 for the October examination and on or before January 1 for the February examination

Application forms may be obtained from Dr William S Middleton, secretary-treasurer, 1301 University Avenue, Madison, Wis

Central Society for Clinical Research—The eleventh annual meeting of the Central Society for Clinical Research will be held in Chicago, Nov 4 and 5, 1938 The Drake Hotel will be the headquarters Information regarding the meeting may be procured from the secretary-treasurer, Dr Lawrence D Thompson, 319 Chase Building, 4932 Maryland Avenue, St Louis The meetings will be open to the public

Book Reviews

Les recto-colites ulcéreuses de cause inconnue By Jean Coste, Ancien
Externe des Hôpitaux de Paris Price, 26 francs Pp 116 Paris Gaston
Doin & Cie, 1937

This is a review of the subject of ulcerative colitis. The author groups the various ulcerative intestinal conditions other than tuberculosis and amebiasis under this general heading. The monograph is largely a review of the experiences of others, with the exception of a short final chapter on treatment with vitamin A. While the material constitutes an excellent review of the subject, the order of presentation is different from that usually employed in this country. The subject is handled as follows: The first chapter is on the history, the second is an introduction to the subject, the third is a clinical study, including a series of reports of cases, the fourth concerns the physical examination, the fifth, the clinical forms of the disease, the sixth, complications, the seventh, diagnosis, the eighth, pathologic anatomy, the ninth, etiology and pathogenesis, and the tenth, treatment.

In the chapter on the history of ulcerative colitis the author traces the origin of the disease to the report by Samuel Wilks in 1873 and then briefly reviews the work of Allchin (1885), Hale White (1888), Mayo-Robson (1893), Boas (1903), Lockhart-Mummery (1904), Hale White (1907-1909), Segond, Cade, Hutinel and Nobécourt (1912), Schmidt (1913), and Bensaude (1919). Under contemporary contributions he mentions especially the work of Bensaude and Antoine, of France, and emphasizes the authoritative studies of Schmidt, of Germany, Udaondo, of South America, Gallart-Mones, of Spain, Hurst, of England, and Bergen, of North America. He calls attention to the discussion of this disease given before the First International Congress in Brussels, in 1935.

In his introduction Coste stresses the importance of an accurate name for so-called ulcerative colitis. He states that in the absence of an accurate designation his study of the disease has been concerned largely with localization, definition of the clinical syndrome, prognosis and an attempt to give an exact description of the condition in the absence of a proved etiologic factor.

In his clinical study the author stresses the fact that ulcerative colitis is a form of dysentery with an insidious or abrupt onset. The important symptoms include painful, bloody evacuations, which frequently first are attributed to hemorrhoids. In the more severe forms fever is common. A large and interesting series of reports of cases is presented.

In the chapter on examination Coste stresses the importance of general physical, rectal and endoscopic examinations. He classifies the conditions into catarrhal, proliferating and intermediary types. The evaluation of the disease is presented graphically. He divides the clinical forms of the disease as follows: (I) according to evolution, into (1) very severe (often fatal), (2) of sudden onset, (3) chronic, (4) abortive and (5) only symptomatic, with subdivision of the symptomatic forms into (a) sanguinopurulent, (b) hemorrhagic and (c) purulent, (II) according to method of attack of the disease, (III) according to localization, into (1) local, which is subdivided into disease of (a) the rectosigmoid, (b) the cecum and ascending colon and (c) the transverse colon, and (2) diffuse, and (IV) according to age, into disease (1) of infants and (2) of persons in middle life.

In the chapter on complications the author reviews the experiences of others, mentioning particularly the detailed review of the cases reported from the Mayo Clinic. The chapter on diagnosis emphasizes the importance of examining the stools and of sigmoidoscopic and roentgenologic studies. Coste stresses the importance of differential diagnosis from neoplasms, polyps, diverticulitis, rectal gonorrhea, hemorrhoids, proctitis, amebiasis and bacillary dysentery.

Under pathologic anatomy an excellent description, as gained from the literature, is given. In the chapter on etiology and pathogenesis the author reviews, first, the reports on the relation of the organisms of bacillary dysentery to this disease and concludes that the evidence of their causal relation is not at hand. He discusses the hypothesis of a single etiologic factor, mentioning the work of Bergen, Gallert-Mones, of Spain, and Butiaux and Sevin, of France, stressing that each confirms the other in part. He feels that a multiple bacterial etiologic factor should be considered.

The chapter on treatment is divided into five subheadings. Under the first is considered specific therapy. Administration of antidyentery serum is discussed as eliminative treatment. Coste stresses the fact that there is not enough evidence of a causal relation. He mentions the serums and vaccines prepared from the various forms of streptococci, stressing the use of the streptococcus vaccine advocated by Bergen and the polyvalent vaccine advocated by Surmont. The second subheading is concerned with symptomatic treatment, under which the author discusses intestinal lavage as indicated under special conditions, saying only that on occasions lavage will irritate and traumatize the intestine. He mentions the use of neosphenamine and of calcium and parathyroid extract, as advocated by Haskell and Cantarow. He suggests the employment of medicine for the production of shock, such as the antidyentery serum of Hurst, some vaccines and anaphylactic substances, such as those mentioned by Kalk. Under the third subheading he mentions the use of mineral waters. Material under the fourth subheading indicates that the aim of the surgical attack should be either diversion of the fecal current or resection of the intestine. Under the fifth subheading are discussed the author's studies and those of his colleagues on vitamin A therapy. He stresses the fact that the treatment is on a symptomatic and not an etiologic basis.

The monograph is well worth reading from the standpoint of a concise and rather critical review of this subject.

Gastroscoy By Rudolf Schindler. Price, \$7.50. Pp. 343, with 89 figures and 96 colored plates. Chicago: University of Chicago Press, 1937.

Schindler has met a pressing need for a book in English dealing with the subject of gastroscoy.

It is fitting that due credit should be given the author for his outstanding work in developing the present efficient flexible gastroscope and for his pioneer work in stimulating interest in this increasingly important diagnostic procedure.

The book reflects the enthusiasm of the author regarding the importance of gastroscoy in the diagnosis of gastric disease. The subject is presented in an interesting manner, and the book may be used not only as a guide to the neophyte in the field of gastroscoy but also as a source of stimulation to all those interested in the domain of gastroenterology.

The first portion of the book deals with the historical development of gastroscoy and the anatomic difficulties involved. This is followed by a painstaking description of the technic of the procedure. The main portion of the book is given over to a description of the gastrosopic appearance in the various forms of gastric disease and their treatment. This has been based primarily on the observations of the author, but careful reference is made to differences of opinion that exist among workers in this field.

One of the most interesting subjects dealt with is that of gastritis and its various subdivisions. Attention is correctly called to the fact that one of the greatest difficulties in dealing with the subject is to determine the limits of the changes that may occur in the normal gastric mucosa. There may be room for doubt in the author's statement that by means of gastroscoy one can absolutely determine the operability of carcinoma of the stomach and that exploratory laparotomy is not a justifiable procedure.

In the discussion of the relation of gastroscoy to other diagnostic procedures, one cannot help feeling that in his enthusiasm the author has not given other

procedures as much credit as they deserve. One might also question the wisdom and necessity of regarding gastroscopy as a routine diagnostic procedure, especially when the diagnosis has been established by other means.

Probably one of the most valuable and instructive parts of the book is the collection of beautiful colored drawings of the gastroscopic appearance in various diseases and conditions that may occur in the stomach.

The book, all in all, is very instructive and well presented and should be studied by all those interested in gastroscopy and the diagnosis of gastric disease.

The Harvey Lectures, Delivered Under the Auspices of the Harvey Society of New York, 1936-1937, Series 32 Price, \$4 Pp 245 Baltimore Williams & Wilkins Company, 1937

This last collection of lectures presented before the Harvey Society comprises eight essays, four of them bearing on important newer developments in the physiology of the nervous system. Wilder Penfield describes his electrical exploration of areas of the cerebral cortex of man and his first provocation of vocalization by this means and gives his views on epilepsy, dream states and automatism. An interesting conclusion is that all parts of the brain may be involved in normal conscious processes, but the indispensable substratum of consciousness lies outside the cerebral cortex, probably in the diencephalon.

The lecture of S. Walter Ranson deals with exploration of the hypothalamus, which led to the conclusion that this part of the brain, by way of the hypothalamico-hypophyseal tract, controls the rate of elimination of water and that through its connection with the rest of the brain and spinal cord the hypothalamus activates the sympathetic system and also, though less directly, the somatic motor centers. Its stimulation or release from cortical control provokes the picture of emotional excitement and, conversely, its suppression is followed by emotional stolidity.

The lecture of Herbert S. Gasser is concerned with action currents in the nerves and excitation in the nervous system. Sir Henry Dale describes the part played by acetylcholine in the transmission of nervous effects through the ganglionic synapses, with particular reference to the objections encountered and the explanations for many of these.

Other lectures in the book are as follows: "The Passage of Fluid Through the Capillary Wall" by Eugene M. Landis, "The Investigation of Intermediary Metabolism with the Aid of Heavy Hydrogen" by Rudolf Schoenheimer, "The Scientific Work of the Health Organization of the League of Nations" by Thorvald Madsen, director of the Serum Institute, Copenhagen, and "The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes" by C. N. H. Long.

Many of these essays sooner or later probably will be regarded as classics, and physicians will be well repaid for time spent on their careful perusal.

Not So Long Ago A Chronicle of Medicine and Doctors in Colonial Philadelphia By Cecil K. Drinker, M.D. Price, \$3.50 Pp 183, with 20 illustrations New York Oxford University Press, 1937

The native Bostonian is generally supposed to be a provincial person with a time-honored prejudice in favor of old things that have been established for a good many years and that do not change too rapidly—things like Harvard College, the symphony concerts or the Lowell Lectures. The native Philadelphian almost always can understand the Bostonian point of view, for he too has an inherited prejudice toward old things and likes to recall the days when persons of gentle birth realized the responsibilities entailed in being known as ladies and gentlemen.

"Not So Long Ago" is a charming book. It has about it the flavor of old Madeira and will appeal to any one with a nice palate, particularly any one entertained by the foibles of the dyed-in-the-wool Bostonian or Philadelphian.

Mrs. Elizabeth Drinker was a great lady of Philadelphia. She became associated through marriage with the Drinkers of Beverly who moved to Philadelphia before Philadelphia was there. It is her diary that has been edited by her great,

great grandson, who, by the grace of God, has returned to New England from Philadelphia and has lately presented excerpts from her diary to Boston as the basis of his series of Lowell Lectures

The diary was written through the eventful years between 1758 and 1807. The editor has placed especial emphasis on what Mrs. Drinker observed of medicine, doctors and hygiene. She knew a good deal of obstetrics, she was familiar with tuberculosis, typhoid, smallpox and yellow fever, she served tea to Dr. Rush in the "parlor" and found his conversation agreeable, and she commented shrewdly on the peculiarities of other medical men, like Dr. Physick, Dr. Kuhn and Dr. Redman. The editor has been skilful in making Mrs. Drinker a thoroughly lively lady. He has selected interesting illustrations with which to embellish her diary. Her views on life in general seem close at hand. At the end of 1781, at the beginning of the "First New Deal," she wrote, "'Tis a bad Gouvernement under which we are liable to have our Houses seachd and every thing laid open to ignorant fellow prehaps thieves." To many of her readers those days will indeed seem not so long ago.

The Technic of Local Anesthesia By Arthur E. Hertzler. Sixth edition. Price, \$5. Pp 284, with 142 illustrations. St. Louis: C. V. Mosby Company, 1937.

The sixth edition of this work includes a consideration of the few good anesthetics that are available for local anesthesia, the dosages and the methods of use, the combination of epinephrine with local anesthetics and the combination of local and general anesthesia. There is a description of the syringes and needles recommended for this work and of various other apparatus which is conveniently employed. The various blocks are described on an anatomic basis, as, for example, in chapter 4, local anesthesia for operations on the scalp, the cranium and its contents, and in chapter 5, local anesthesia for operations on the face, jaw and tongue. In the following chapters local anesthesia is described with respect to operations on the ear and mastoid cells, operations for trifacial neuralgia and operations on the fifth cranial nerve, cervical lymph nodes, buccal soft parts, thyroid gland, tonsils, larynx, trachea, mammary gland, thorax, lungs, spinal column and abdomen. Paravertebral and splanchnic anesthesia are dealt with in a chapter, as well as sacral and transsacral block anesthesia. There is a special chapter on spinal anesthesia, written by Dr. Irene A. Koeneke, this subject being considered in considerable detail. There are further chapters on local anesthesia for operations for inguinal and femoral hernias and also for umbilical and scar hernias and hernia of the linea alba and for operations on the penis, scrotum, urethra, bladder, prostate gland, female organs, rectum and upper and lower extremities. There is a short chapter on the intravenous use of sodium amytal, which has not been employed much clinically as a surgical anesthetic since 1930. The subject of preliminary medication is discussed briefly. This is a very useful book for the general surgeon because the author's preference is infiltration of tissue to be incised, which is the most effective method for use by the general surgeon unless he has been trained also in the methods of obtaining regional anesthesia. There are one hundred and forty-two excellent illustrations.

Practical Talks on Kidney Disease By Edward Weiss, M.D., Professor of Clinical Medicine, Temple University School of Medicine. Price, \$3. Pp 176, with 10 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

This is an unpretentious, friendly little book that is well worth knowing. The author says that he had an attack of glomerular nephritis during his internship and ever since has been especially interested in renal disease. Evidently, too, he has also been interested in physicians. He has put together this volume "to assist the physician who practices general medicine to understand what is generally regarded as a difficult and confused subject."

The plan of the book is sensible. Renal physiology and tests of renal function are first discussed, next the signs and symptoms of renal disease are considered

and finally the various major forms of Bright's disease are elaborated on under the chapter headings glomerulonephritis, nephrosis, pregnancy and kidney disease and nephrosclerosis

The author knows of what he writes and is familiar with the literature. His style is clear, he drives home simple truths, for instance, that nowadays the general practitioner must not be afraid of the ophthalmoscope. He paints a clear picture of what is generally believed regarding renal disease and its treatment and remains properly skeptical about the newer therapeutic procedures that are still under fire, such as the use of acacia in the management of edema or various operations on the sympathetic nervous system to cure hypertension.

The title of the book is a good description of its contents. Certainly here is a series of exceptionally practical talks on the modern problems of renal disease which many physicians, both old and new, will enjoy.

The Postmortem Examination By Sidney Farber, M.D., Associate in Pathology, Harvard Medical School. Price, \$3.50. Pp 201, with 33 illustrations. Springfield, Ill. Charles C. Thomas, Publisher, 1937.

Nowadays, with the problem of adequate postgraduate medical education looming large on the horizon and with meticulous clinicopathologic correlation becoming increasingly important to clinicians and pathologists in medical schools, teaching hospitals and the better administered smaller hospitals, it is timely to have published a book dealing with the postmortem examination.

This new handbook is an excellent one, well constructed, well written, well illustrated and informative from beginning to end. There is a nice historical introduction to please the historical minded, and, better still, at the end is reprinted a protocol by Virchow which is a model of gross pathologic description. The bulk of the volume discusses pathologic technique in simple and clear terms, explaining the various procedures to be employed in a properly conducted necropsy.

There are twelve chapters in the book, and at the end of each is a short list of references to supplementary matter which should appeal to students. Finally there are given tables of average weights of organs compiled from various authoritative sources and a copy of the report of the New York committee on rules governing pathologists and undertakers. The latter is a useful document, which was included in the hope that it might "serve as a guide for similar committees in other cities of the United States."

On the whole, Virchow, Chiari, Warthin and Mallory and Wright should graciously welcome this newcomer, it will prove a respectable member of the Society of Good Books and, before long, much thumbed in all medical and hospital libraries, will occupy an honorable position on the same shelf with these distinguished predecessors.

Physical Diagnosis. By Don C. Sutton, M.D. Price, \$5. Pp 495, with 298 illustrations and 8 colored plates. St. Louis. C. V. Mosby Company, 1937.

So many excellent books on physical diagnosis have appeared recently, especially that of Major, in addition to the innumerable old standbys, that one wonders whether this new volume displays any original features. Perhaps the outstanding part is the illustrations, which are unusually good and are well selected to illustrate problems of physical diagnosis. The reviewer hesitates to say, however, that this new book is either better or worse than most of its predecessors.

Erforschung und Praxis der Wärmebehandlung in der Medizin einschliesslich Diathermie und Kurzwellentherapie Edited by B. Rajewsky, M.D., and H. Lampert, M.D. Price, 9.50 marks. Pp 185, with 82 illustrations. Dresden. Theodor Steinkopff, 1937.

Twelve papers which were read before the second conference on medical science at Frankfurt, Germany, on the present status of heat therapy are included in this volume, together with a great deal of the discussion relative to them. The

papers deal with the practical or therapeutic use of heat, physiologic principles and the physical nature of the instruments used and the energy emitted by them. The last five papers will be of interest to various specialists, as they deal with the use of heat treatment in internal medicine, pediatrics, surgery, gynecology and balneology. The practitioner of physical therapy who is interested in knowing what he is doing when he uses heat will obtain much valuable information from a study of these articles.

Differentialdiagnose in der inneren Medizin III By Prof Dr Med O Naegeli. Price, 10 80 marks. Pp 415 to 772, with 59 illustrations. Leipzig Georg Thieme, 1937.

This volume is the third instalment of Naegeli's work on differential diagnosis. The febrile diseases and diseases of the joints, esophagus, heart, kidneys, nervous system and internal secretory glands are discussed. The book is beautifully illustrated and contains a mine of useful material. To the reviewer, however, it seems that differential diagnosis does not lend itself well to treatment as an independent subject, in fact, much of the matter given here is simply a duplication of what is found in general textbooks of medicine.

The Human Mind By Karl A Menninger. Second edition. Price, \$5. Pp 504. New York Alfred A Knopf, 1937.

Dr Menninger has produced a solid yet readable book, and the profusion of brief case histories, graphically presented, will undoubtedly appeal to the lay reader. Just what, if any, purpose is served, however, by attempting to initiate the general public into the mysteries of psychiatry is another question. Had Pope lived today, he surely would have had this question in mind when he warned "Drink deep, or taste not the Pierian spring." Every one knows that the newspaper reader promptly worries about having all the symptoms enumerated in the patent medicine advertisements, may not a similar and perhaps more serious disturbance result from reading popular psychiatry?

Tuberculose du tube digestif By A Cade, P Santy and J Heitz. Price, 80 francs. Pp 410, with 27 illustrations. Paris Gaston Doin & Cie, 1937.

This book is one of a series of monographs on tuberculosis published by the Bibliotheque de la tuberculose, founded by Chantemesse, Poncet and Collet. Tuberculosis of the gastrointestinal tract has been investigated intensively in recent years, and this volume constitutes a review of the laboratory and clinical development in this field. Theory is given due consideration, but particular attention is paid to treatment, including surgical procedures. An extensive bibliography adds greatly to the usefulness of this book.

Les hépatites By Maurice Loeper, M D. Price, 60 francs. Pp 262, with 47 illustrations. Paris Masson & Cie, 1937.

In this monograph the author deals systematically with various forms of hepatitis. There is much interesting material, but the classification of the various types does not seem entirely clear or satisfactory. However, the reports of cases make it possible for those accustomed to other classifications to follow fairly well the author's views. A considerable bibliography is included.

Allgemeine Elektrodiagnostik By Prof Dr Eberhard Koch. Second edition. Price, 3 marks. Pp 40, with 37 illustrations. Dresden Theodor Steinkopff, 1937.

This little outline reduces to forty pages the essentials of electrocardiography with the aid of excellent charts and diagrams.

ACTION OF DIGITALIS IN COMPENSATED HEART DISEASE

HAROLD J STEWART, M D

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AND

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NEW YORK

A report¹ has already been made concerning certain effects on the circulation caused by the giving of therapeutic amounts of digitalis to normal persons and to patients suffering from organic heart disease who exhibit signs and symptoms of congestive heart failure. In the case of the normal heart, the action of digitalis was to decrease its size and the volume of its output of blood per minute,¹ in the case of the enlarged heart, whether the rhythm was regular or that of auricular fibrillation, the action was to decrease its size and to increase its output of blood per minute.² There was one action of digitalis which was common to the normal and to the enlarged heart, namely, the effect on size, which was to decrease it. We were led, then, to the notion that this action was an essential one and that the cardiac output which resulted depended on the initial size of the heart. Moreover, the effect on the size of the heart appeared to be due to an action of the drug on the cardiac muscle, since we were unable to show that the decrease in the size of the heart and the decrease in cardiac output which we observed were associated with a decrease in venous pressure.¹ Moreover, results parallel to these were found when observations were made on normal

From the New York Hospital and the Department of Medicine, Cornell University Medical College

An abstract of these studies was presented before the American Society for Clinical Investigation, Atlantic City, N J, May 6, 1935

1 Stewart, H J, and Cohn, A E. III. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart, *J Clin Investigation* **11** 917 (Sept) 1932

2 (a) Stewart, H J, Detrick, J E, Crane, N F, and Wheeler, C H. Action of Digitalis in Uncompensated Heart Disease, *Arch Int Med*, this issue, p 569. (b) Stewart and Cohn.¹

dogs,³ as well as on dogs with large hearts without failure.⁴ The results so far as cardiac output was concerned were similar to those reported by Burwell, Neighbors and Regen⁵ (for normal human beings) and by Harrison and Leonard⁶ (for normal dogs).

In continuing the study of the action of digitalis we observed the effect of giving the drug to patients suffering from organic heart disease who had not experienced congestive heart failure. Studies were made not alone of patients with a regular rhythm but also of those exhibiting auricular fibrillation. There was reason, as a matter of fact, for observing the action of digitalis in those patients exhibiting normal rhythm, since Christian⁷ has advocated its use in these cases.

I OBSERVATIONS ON PATIENTS EXHIBITING NORMAL SINUS RHYTHM

We wished to reduce our observations to as standardized a procedure as possible in order to compare the results obtained in different patients. To this end we chose, in the first place, for this part of the study only those subjects who satisfied the following criteria: (a) All the patients exhibited signs of organic valvular disease of rheumatic origin, (b) patients were chosen who had not suffered from an attack of congestive heart failure or who did not have heart failure at the time of observation, (c) the patients had heart disease either of type I (activity not limited) or of type IIA (activity slightly limited), as described in the publication entitled "Criteria for the Classification and Diagnosis of Heart Disease" issued by the Heart Committee of the New York Tuberculosis and Health Association,⁸ (d) patients were given within twenty-four hours the same amount of digitalis, namely 1.6 to 1.8 Gm. of the same "batch."⁹

3 Cohn, A. E., and Stewart, H. J. The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs, *J. Clin. Investigation* **6**: 53 (Aug.) 1928.

4 Cohn, A. E., and Stewart, H. J. The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Dogs in Which the Heart Is Enlarged, *J. Clin. Investigation* **6**: 79 (Aug.) 1928.

5 Burwell, C. S., Neighbors, DeW., and Regen, E. M. The Effect of Digitalis upon the Output of the Heart in Normal Man, *J. Clin. Investigation* **5**: 125 (Dec.) 1928.

6 Harrison, T. R., and Leonard, B. W. The Effect of Digitalis on the Cardiac Output of Dogs and Its Bearing on the Action of the Drug in Heart Disease, *J. Clin. Investigation* **3**: 1 (Oct.) 1926.

7 Christian, H. A. The Use of Digitalis Other Than in the Treatment of Cardiac Decompensation, *J. A. M. A.* **100**: 789 (March 18) 1933.

8 Criteria for the Classification and Diagnosis of Heart Disease, ed. 2, New York, New York Tuberculosis and Health Association, 1929.

9 Experience with this particular "batch" showed that this amount was required regardless of body weight to slow the rapid ventricular rate in the presence of auricular fibrillation to around 70 per minute when given within twenty-four hours, it was considered as the "digitalizing" amount (unpublished data).

prepared and standardized by the American Heart Association. To all the patients the total amount was distributed during the day in approximately the same fashion, as follows: 0.8 Gm at 8 or 9 a. m., 0.5 Gm at noon or 1 p. m., 0.3 Gm at 4 p. m. and 0.2 Gm at 8 or 9 p. m. And finally, in the third place, observations were made at the same time with respect to the giving of digitalis. On the first day (see section on methods) observations on the circulation were made. On the next day digitalis was given, the first dose was administered early in the morning and the total amount by evening. On the next day, twenty-four hours after treatment with digitalis was started, observations were repeated and then again twenty-four or forty-eight hours later and in certain cases at still longer intervals. Since our other observations demonstrated that the early effects of digitalis were important, we made measurements twenty-four hours after use of the drug had been started.¹

In addition to observations relating to rheumatic heart disease (cases 1 to 13, inclusive), data were also obtained concerning patients with hypertensive (case 14), arteriosclerotic (cases 15 and 16) and syphilitic (case 17) heart disease.

Methods—The methods and plan of procedure used in making these observations, as well as those to be reported in our next paper,² were as follows:

All observations were made in the morning while the patient was in a basal metabolic state. Measurements of the cardiac output were made by the acetylene method, three samples of gas being taken, as recommended by Grollman¹⁰ in his book entitled "The Cardiac Output of Man in Health and Disease," and as further elaborated by Grollman, Friedman, Clark and Harrison.¹¹ During this measurement the patient sat in a steamer chair (at an angle of 135 degrees) with the legs extended. Each patient was made familiar with and trained to carry out the procedures beforehand. While he was resting quietly, the radial pulse was counted at intervals of five minutes. At the end of one-half hour the acetylene-air-oxygen mixture was rebreathed. The amount of gas in the "rebreathing bag" was adjusted to the amount the patient could take satisfactorily. Three samples of gas were obtained during each period of rebreathing for estimation of the arteriovenous oxygen difference. Three periods of rebreathing were carried out to make certain that mixing was secured, one, two or all sets were analyzed. Shortly afterward the oxygen consumption was measured with a Benedict-Roth spirometer. After a short pause the vital capacity was measured, and the height and the weight were recorded. Then the patient rested again, this time by lying down. In succession, sufficient time being allowed between each procedure for the patient to return to a basal metabolic state, an electrocardiogram was taken, the

10 Grollman, A. The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 73.

11 Grollman, A., Friedman, B., Clark, G., and Harrison, T. R. Studies in Congestive Heart Failure. XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12** 751 (Sept.) 1933.

arm to tongue circulation time recorded, the venous pressure estimated and the blood pressure measured, finally, the basal state still being maintained, a roentgenogram of the heart was made at a distance of 2 meters

The arm to tongue circulation time was estimated by the use of decholin sodium, 5 cc of a 20 per cent solution was injected rapidly (one to two seconds) through an 18 gage needle into an antecubital vein while the patient was lying quietly in a supine position. This was repeated one and one-half minutes after the response to the first test had been elicited. The time was recorded from the beginning of the injection until the patient perceived the bitter taste. The injection time was also recorded, since, however, the response may come with a minimal amount of the drug, the time which we used was measured from the start rather than from the conclusion of the injection.

The venous pressure was measured by the direct method,¹² a large antecubital vein being used and the arm being placed on a level with the right auricle. The apparatus consisted of an L tube of glass attached to a three way stopcock, a syringe and an 18 gage needle. The apparatus was filled with a sterile normal solution of sodium chloride, venipuncture was performed and the direct pressure readings were recorded. Normal pressures with this apparatus range from 4 to 9 cm of saline solution. The antecubital vein of one arm was reserved for the injection of decholin and that of the other arm for the measurement of venous pressure. In subsequent measurements the vein was entered at the site first punctured.

Roentgenograms of the cardiac silhouette were taken with the patient in the standing position, during full inspiration, at a distance of 2 meters.¹³ Measurements of the cardiac area were carried out by the technic of Levy,¹⁴ and estimations of volume were made as recommended by Bardeen.¹⁵ The volumes recorded in table 1 were not multiplied by the constant which is included in Bardeen's formula. This was omitted in order to make our observations comparable to those of Starr.¹⁶

The work of the left ventricle per beat was calculated by making use of the formula¹⁷ $W = QR + \frac{wV^2}{2g}$, in which W equals the work done per beat, Q equals the volume of blood expelled per beat, R equals the mean arterial blood pressure in millimeters of mercury times 136, V equals the velocity of blood in the aorta, w equals the weight of the blood, and g equals the acceleration due to gravity. The last part of the formula, $\frac{wV^2}{2g}$, was omitted.¹⁶

Observations—According to the results obtained for 13 patients suffering from rheumatic heart disease, three groups were made with

12 Taylor, F A, Thomas, A B, and Schleiter, H G. A Direct Method for the Estimation of Venous Pressure, *Proc Soc Exper Biol & Med* **27** 867 (May) 1930.

13 The staff of the Roentgenologic Department of the New York Hospital cooperated in this investigation.

14 Levy, R L. The Size of the Heart in Pneumonia. A Teleoroentgenographic Study, with Observations on the Effect of Digitalis Therapy, *Arch Int Med* **32** 359 (Sept) 1923.

15 Bardeen, C R. Determination of the Size of the Heart by Means of X-Rays, *Am J Anat* **23** 423 (March) 1918.

16 Starr, I, Jr, Collins, L H, Jr, and Wood, F C. Studies of the Basal Work and Output of the Heart in Clinical Conditions, *J Clin Investigation* **12** 13 (Jan) 1933.

17 Starling, E H. Principles of Human Physiology, ed 6, Philadelphia, Lea & Febiger, 1933, p 772.

respect to the effect of digitalis on the cardiac output In 4 cases (case 1 to 4) its effect was to decrease the cardiac output (group 1) and in 3 (cases 5 to 7) to increase the cardiac output (group 2), finally, in 6 cases (cases 8 to 13) no change in cardiac output was observed (group 3)

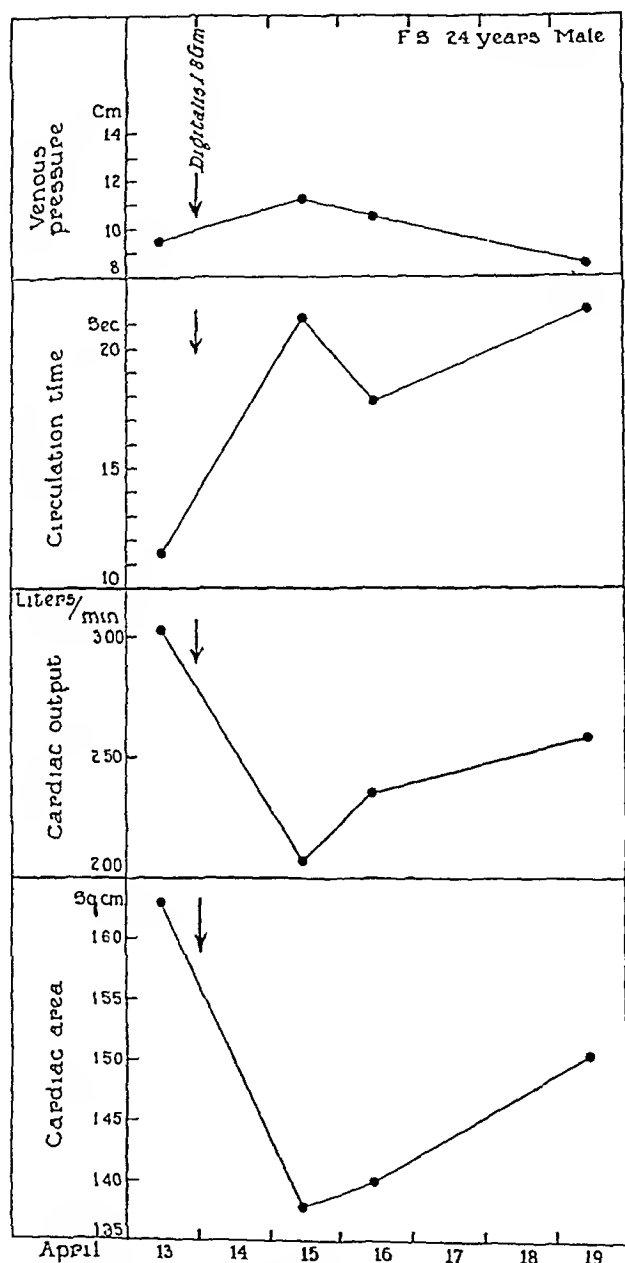


Fig 1 (case 1) —The effect of digitalis on the cardiac output, cardiac size, venous pressure and circulation time of F S, representing group 1

Group 1 Decrease in Cardiac Output Case 1 illustrates the effect of digitalis in this group of patients After the administration of 1.8 Gm of digitalis there occurred within twenty-four hours a decrease in cardiac output per minute (table 1 and figs 1 and 2) and per beat, a

TABLE 1—Data Relating to the Effect of Digitalis in Seventeen Cases

Case	Age	Sex	Date	Body Surface, Sq M	Oxygen Consumption, Cc per Min	Arterio-venous Oxygen Difference, Cc	Cardiac Output, L per Min	Cardiac Output, Sq M per Min	Cardiac Area, Sq Cm	Cardiac Volume, Cc †	Arterial Pressure, Mm Hg	Circulation Time, Sec
Rheumatic Heart Disease Group 1 Decreased Cardiac Output												
1 F S	24	M	4/13/35	1 58	195	64 6	3 02	1 91	162 9	1,897	106/66	11 5
			4/14/35			86 9	2 07	1 31	138 0	1,463	112/76	21 3
			4/15/35	1 58	180	77 3	2 35	1 48	140 5	1,535	102/62	17 8
			4/16/35	1 53	182	72 4	2 58	1 63	150 5	1,690	132/70	21 6
			4/19/35	1 53	187							
2 A G	23	M	10/30/34	1 73	210	69 9	3 00	1 74	144 0	1,570	118/80	16 0
			11/12/34	1 75	214	69 7	3 06	1 79	141 9	1,530	118/74	18 5
			11/13/34			86 5	2 47	1 43	122 0	1,273	118/72	19 7
			11/14/34	1 73	214	88 6	2 41	1 40	117 6	1,170	118/72	20 0
			11/16/34	1 72	214	76 8	2 81	1 63	123 8	1,265	103/70	17 5
			11/17/34	1 72	216							
3 M R	32	F	4/ 4/34	1 45	158	89 6	1 76	1 21	154 4	1,745	115/55	
			4/ 5/34									
			4/ 6/34	1 44	160	115 5	1 39	0 97	135 7	1,415	110/64	
			4/ 7/34	1 44	160	109 3	1 46	1 01	130 2	1,350	105/65	
			4/14/34	1 44	151	101 8	1 48	1 03	139 6	1,515	120/70	
4 C W	25	M	12/ 7/35	1 92	290	73 4	4 00	2 03	273 6	4,120	102/54	24 0
			12/19/35	1 94	286	75 8	3 77	1 95	273 2	4,120	116/66	25 2
			12/20/35									
			12/21/35	1 90	267	89 5	2 98	1 57	248 9	3,530	103/65	25 7
			12/23/35	1 92	290	84 6	3 43	1 78	253 7	3,680	104/60	22 4
Group 2 Increased Cardiac Output												
5 E P	21	M	11/ 8/34	1 54	195	71 4	2 73	1 77	119 2	1,186	122/50	19 5
			11/ 9/34									
			11/10/34	1 55	185	60 4	3 07	1 93	99 8	910	120/50	14 7
			11/13/34	1 55	185	54 0	3 43	2 21	114 7	1,108	120/60	13 8
			11/15/34	1 55	190	60 4	3 14	2 03	114 8	1,108	120/50	15 3
6 M C	46	F	12/10/34	1 44	182	77 4	2 35	1 63	125 8	1,280	128/84	15 6
			12/11/34									
			12/12/34	1 44	177	77 0	2 30	1 60	131 0	1,365	120/68	17 6
			12/13/34	1 44	183	62 8	2 91	2 02	120 8	1,217	123/68	17 1
			12/18/34	1 44	191	67 2	2 84	2 00	111 7	1,076	118/69	20 7
7 R D	28	F	10/20/34	1 70	233	68 6	3 40	2 00	146 0	1,640	106/70	17 5
			10/21/34									
			10/22/34	1 70	218	47 8	4 56	2 62	132 4	1,380	108/66	13 7
			10/30/34	1 70	230	52 2	4 41	2 59	135 0	1,450	116/70	13 3
Group 3 No Change in Cardiac Output												
8 R L	21	M	4/ 6/35	1 75	234	70 9	3 30	1 89	120 6	1,220	120/64	17 2
			4/ 7/35									
			4/ 8/35	1 75	234	70 9	3 30	1 89	122 6	1,250	130/78	16 9
			4/ 9/35	1 76	230	74 0	3 11	1 77	119 3	1,200	124/70	17 4
9 J F	21	F	5/18/35	1 48	122	65 9	1 85	1 25	121 6	1,220	104/50	16 6
			5/19/35									
			5/20/35	1 49	131	67 1	1 96	1 31	120 5	1,208	104/68	15 5
			5/22/35	1 49	131	65 4	2 00	1 34	124 5	1,265	104/58	15 1
10 E C	19	F	3/18/35	1 66	195	82 8	2 36	1 42	106 9	1,040	104/10	10 7
			3/19/35									
			3/20/35	1 68	195	82 7	2 36	1 40	104 7	935	118/40	13 7
			3/21/35	1 68	189	82 2	2 30	1 37	101 6	825	120/ 0	12 3
11 A M	23	F	2/14/35	1 73	203	62 7	3 24	1 87	97 6	886	112/56	11 6
			2/15/35									
			2/16/35	1 71	205	61 9	3 31	1 94	95 3	887	120/50	13 7
12 J S	28	F	10/ 8/34	1 81	256	61 1	4 19	2 31	125 0	1,265	110/75	12 9
			10/ 9/34									
			10/10/34	1 81	256	60 9	4 20	2 32	125 6	1,280	122/66	11 5
			10/11/34	1 81	259	65 3	3 97	2 20	123 7	1,265	110/60	12 7
13 R M	21	F	9/19/34	1 46	185				180 6	2,210	130/70	
			9/27/34	1 46	189	109 1	1 73	1 19	181 3	2,210	115/75	
			9/29/30/34									
			10/ 1/34	1 44	193	106 0	1 82	1 26	175 6	2,120	90/70	
			10/ 2/34	1 44	191	109 2	1 75	1 22	180 0	2,200	110/80	
			10/ 3/34	1 44	180	101 5	1 76	1 22	172 9	2,030	100/70	
			10/ 6/34	1 46	185	100 8	1 83	1 25	183 3	2,260	110/70	25 0

* In this table, as well as in table 2, the following symbols are used: M S, mitral stenosis; M I, mitral insufficiency; A S, aortic stenosis; A I, aortic insufficiency; Enl Ht., enlarged heart; Rt I V HB, right intra ventricular heart block. The roman numerals indicate the classification number.

† The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text.

of Compensated Cardiac Disease Associated with Normal Rhythm

Venous Pressure, Cm	Vital Capacity, Cc	Cardiac Rate, per Min	Cardiac Output, Cc per Beat	Work of Left Ventricle, Gm per Beat	Digitalis, Gm	Age at Which Rheumatic Infection Occurred, Yr	Age at Which Cardiac Lesion Was Diagnosed, Yr	Age at Onset of Symptoms, Yr	Symptoms	Diagnosis	Red Blood Cell Count and Hemoglobin Value†
Rheumatic Heart Disease Group 1 Decreased Cardiac Output											
9.5	4,400	72	42	49	1.8	8 chorea 12 joints	Unknown	10	Occasional dyspnea	M S, M I, Enl Ht, I	4.4 80
11.2	4,100	72	29	37							
10.5	4,000	72	33	37							
8.5	4,200	60	43	59							
	4,200	76	39	53		? 10	Unknown	23	Fatigue	M S, M I, Enl Ht, I	4.9 85
	4,300	76	40	52							
					1.7						
	4,200	80	31	40							
	4,250	80	30	39							
	4,250	64	44	53							
	2,100	60	29	34	1.6	Unknown	10	27	Dyspnea on exertion	M S, M I, Enl Ht, I	4.7 100
	2,180	65	21	25							
	2,000	72	20	23							
	2,200	58	26	34							
10.5	3,850	70	57	60.5		Unknown	12	3	Slight dyspnea	M S, M I, Enl Ht, I	5.4 94
8.8	4,100	70	54	60.8	1.8						
8.6	4,100	64	47	52.4	0.2 q d §						
10.9	4,100	74	46	51.3							
Group 2 Increased Cardiac Output											
	3,100	80	34	40	1.7	Unknown	Unknown	None	None	M S, M I, A S, A I, Enl Ht, IIA	5.0 100
	3,250	66	47	54	0.2 q d						
	3,250	72	48	59							
	3,200	64	49	56							
6.7	2,600	66	36	52	1.8	44	10	44	Slight dyspnea	M S, M I, A S, A I, Enl Ht, IIA	3.6 79
5.6	2,550	62	37	47							
5.3	2,500	60	48	64							
5.3	2,600	59	48	61							
	2,300	100	34	41	1.8	Unknown	24	24	Slight dyspnea	M S, M I, Enl Ht, IIA	91
	2,450	82	56	68	0.2 q d						
	2,500	82	54	66							
Group 3 No Change in Cardiac Output											
10.5	4,100	74	45	56	1.8	15 joints	Unknown	20	Slight dyspnea on exertion	M S, M I, A I, slightly Enl Ht, I	5.8 102
8.3	4,050	72	46	65	0.3						
13.7	4,200	74	42	55							
6.8	2,800	70	26	27	1.8	Unknown	12	23	Dyspnea on exertion	M S, M I, A S, A I, slightly Enl Ht, I	4.8 90
7.7	3,000	66	30	35	0.2 on May 21						
7.8	3,000	78	27	30							
8.2	2,850	86	27	21	1.8	9 joints and chorea	9	None	None	M S, M I, A S, A I, slightly Enl Ht, I	4.8 90
9.6	2,800	84	29	31		16 joints					
9.1	2,900	80	29	23		18 joints					
10.1	2,900	74	44	52	1.8	6 chorea 15 chorea	Childhood	22	Dyspnea on exertion	M S, M I, A I, Enl Ht, I or IIA	4.8 88
9.5	2,250	72	46	53							
	2,700	118	36	45	1.8	Unknown	24	Childhood	Slight dyspnea on exertion	M S, M I, slightly Enl Ht, I or IIA	75
	2,970	106	40	51	0.2 q d						
	2,850	100	40	47							
	2,350	74				6 joints	6	12	Dyspnea on exertion	M S, M I, A S, A I, Enl Ht, IIA	4.1 85
	2,600	72	24	31	1.7						
	2,525	70	26	29	0.2 q d						
	2,500	64	27	35	0.1 on Oct 5						
	2,500	64	28	32							
	2,500	62	30	36							

† The values for red blood cells are given in millions those for hemoglobin are given in percentages, 14.5 Gm of hemoglobin being equivalent to 100 per cent

§ When maintenance amounts of digitalis were given, the measurements were made in the morning as usual and the maintenance dose of digitalis was given later in the day

TABLE 1—Data Relating to the Effect of Digitalis in Seventeen Cases of Com

Case	Age	Sex	Date	Body Surface, Sq M	Oxygen Consumption, Cc per Min	Arterio-venous Oxygen Difference, Cc	Cardiac Output, L per Min	Cardiac Output, L per Sq M per Min	Cardiac Area, Sq Cm	Cardiac Volume, Cc †	Arterial Pressure, Mm Hg	Circulation Time, Sec
Hypertensive Heart Disease												
14 A G	62	F	3/11/36	1.61	143	65.9	2.17	1.35	118.7	1,180	150/80	15.6
			3/12/36									
			3/13/36	1.61	135	74.4	1.81	1.12	121.7	1,224	140/76	14.6
			3/14/36	1.61	120	63.2	1.76	1.10	113.0	1,095	160/80	17.0
Arteriosclerotic Heart Disease												
15 C Me A	69	M	1/15/35	1.67	259	64.6	4.01	2.40	107.7	1,030	120/60	11.5
			1/16/35									
			1/17/35	1.66	259	74.6	3.47	2.09	92.5	797	118/56	11.9
			1/19/35	1.66	267	60.7	4.40	2.65	100.7	927	124/70	11.5
16 J S	58	M	10/29/35	1.59	160	72.9	2.20	1.38	139.0	1,493	122/82	27.0
			10/30/35									
			10/31/35	1.60	178	52.1	3.42	2.14	126.6	1,297	138/90	24.3
			11/ 6/35	1.57	174	48.3	3.60	2.29	105.1	982	129/78	20.4
Syphilitic Heart Disease												
17 H W	48	M	10/15/34	1.75	227	64.1	3.54	2.02			118/50	13.2
			10/16/34	1.75	232	60.3	3.85	2.20	137.5	1,460	108/40	1.38
			10/17/34	1.75	222	60.1	3.69	2.10	138.5	1,485	118/46	12.8
			10/18/34									
			10/19/34	1.75	228	74.8	3.05	1.74	128.6	1,330	120/40	16.0
			10/23/34	1.75	220	73.5	2.99	1.71	127.3	1,295	130/50	15.1
			10/26/34	1.76	220	77.4	2.84	1.61	129.3	1,330	120/40	16.8

* In this table, as well as in table 2 the following symbols are used: M S, mitral stenosis; M I, mitral insufficiency; A S, aortic stenosis; A I, aortic insufficiency; Enl. Ht., enlarged heart; Rt. I.V.H.B., right intra ventricular heart block. The roman numerals indicate the classification number.

† The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text.

TABLE 2—Data Relating to the Effect of Digitalis in Five Cases of

Case	Age	Sex	Date	Body Surface, Sq M	Oxygen Consumption, Cc per Min	Arterio-venous Oxygen Difference, Cc	Cardiac Output, L per Min	Cardiac Output, L per Sq M per Min	Cardiac Area, Sq Cm	Cardiac Volume, Cc *	Arterial Pressure, Mm Hg
18 H O	73	M	3/ 5/35	1.80	205	97.6	2.10	1.17	224.1	3,055	140/130/ 76
			3/ 6/35								
			3/ 7/35	1.79	222	62.5	3.55	2.00	210.8	2,792	145/ 60
19 M R	25	F	4/11/34	1.52	191	96.2	1.98	1.30	189.8	2,398	98/ 60
			4/20/34	1.52	180	98.2	1.83	1.20	194.4	2,472	98/ 60
			4/21/34								
			4/22/34	1.52	184	84.5	2.18	1.44	178.4	2,172	110/ 80
			4/27/34	1.48	172	83.6	2.06	1.39	185.1	2,315	98/ 60
20 C C	44	F	10/25/34	1.47	218	125.6	1.74	1.18	136.1	1,450	150/100
			10/26/34								
			10/27/34	1.44	189	89.3	2.12	1.45	122.3	1,232	130/ 70
21 J G	28	M	11/12/35	1.55	237	86.3	2.75	1.80	154.3	1,746	135/ 76
			11/13/35								
			11/14/35	1.55	228	81.0	2.81	1.80	157.8	1,805	150/ 78
			11/16/35	1.55	226	86.2	2.61	1.70	143.5	1,567	152/ 76
22 H C	50	M	10/ 1/35	2.13	267	68.2	3.92	1.84	159.3	1,833	120/ 80
			10/ 2/35								
			10/ 3/35	2.13	267	66.1	4.04	1.90	153.0	1,726	118/110/ 84

* The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text.

† The values for red blood cells are given in millions, those for hemoglobin are given in percentages.

*Compensated Cardiac Disease Associated with Normal Rhythm *—Continued*

Venous Pressure, Cm	Vital Capacity, Cc	Cardiac Rate, per Min	Cardiac Output, Cc per Beat	Work of Left Ventricle, Gm M per Beat	Digitalis, Gm.	Age at Which Rheumatic Infection Occurred, Yr	Age at Which Cardiac Lesion Was Diagnosed, Yr	Age at Onset of Symptoms, Yr	Symptoms	Diagnosis	Red Blood Cell Count and Hemoglobin Value†
Hypertensive Heart Disease											
91	1,600	80	27	42	1.8	Unknown	Unknown	45	Slight dyspnea	Rt-I V-HB, not Enl Ht, IIA	37 84
7.8	1,500	70	26	38							
6.8	1,350	66	27	44							
Arteriosclerotic Heart Disease											
5.5	2,700	70	57	70	1.8	Unknown	Unknown	66	Slight dyspnea	M I not Enl Ht, IIA	45 90
5.3	2,500	82	42	50							
5.8	2,500	72	61	80							
3.7	2,600	58	38	53	1.8 0.2 q d	Unknown	Unknown	Unknown	Occasional paroxysmal tachycardia	None not Enl Ht, IIA	49 100
4.9	2,700	56	61	94							
3.8	2,900	64	56	79							
Syphilitic Heart Disease											
	4,100	74	48	55	1.8 0.2 q d	Syphilitic infection at 22	Unknown	None	None	A I, Enl Ht, I	43 84
	4,100	72	53	53							
	4,250	74	49	55							
	4,250	70	48	47							
	4,250	68	43	53							
	4,200	64	44	48							

† The values for red blood cells are given in millions, those for hemoglobin are given in percentages, 14.5 Gm of hemoglobin being equivalent to 100 per cent

§ When maintenance amounts of digitalis were given, the measurements were made in the morning as usual, and the maintenance dose of digitalis was given later in the day

Compensated Cardiac Disease Associated with Auricular Fibrillation

Circulation Time, Sec	Venous Pressure, Cm	Vital Capacity, Cc	Cardiac Rate, per Min	Cardiac Output, Cc per Beat	Work of Left Ventricle, Gm M per Beat	Digitalis, Gm	Diuresis	Diagnosis	Red Blood Cell Count and Hemoglobin Value†
21.2	8.9	3,800	92	23	23.2	1.7	Not measured	M S, M I, Enl Ht, I	
	8.2	3,800	70	51	71.4				
		2,100 2,310	86 106	23 17	24.7 18.5		None	M S, M I, Enl Ht, IIA	42 90
		2,300 2,700	70 70	20 20	28.8 32.2	1.7 0.1 q d			
17.0		1,900	142	12	20.7		None	M S, M I, slightly Enl Ht, IIA	50 100
10.0		2,100	92	23	31.3				
19.9	9.1	2,750	66	42	60.5	1.8 0.1 q d	None	M S, M I; Enl Ht, IIA	
21.2	5.9	2,830	52	54	83.7				
22.1	6.3	2,900	50	52	80.6				
18.5	8.3	3,300	88	45	61.2	1.8	None	Arteriosclerosis, Enl Ht, IIA	52 100
18.8	8.9	3,600	89	52	70.0				

decrease in cardiac size, slowing of the circulation time and no essential change in venous pressure. Reversion toward predigitalis levels occurred as the digitalis effect wore off. Results similar to these were observed in 3 other patients (cases 2 to 4) suffering from rheumatic heart disease, as well as in 1 with hypertensive (case 14), 1 with arteriosclerotic (case 15) and 1 with syphilitic (case 17) involvement (table 1).

Group 2 Increase in Cardiac Output Case 5 illustrates the effect of the drug in this group. Twenty-four hours after the giving of 1.7 Gm of digitalis there occurred an increase in cardiac output per minute and

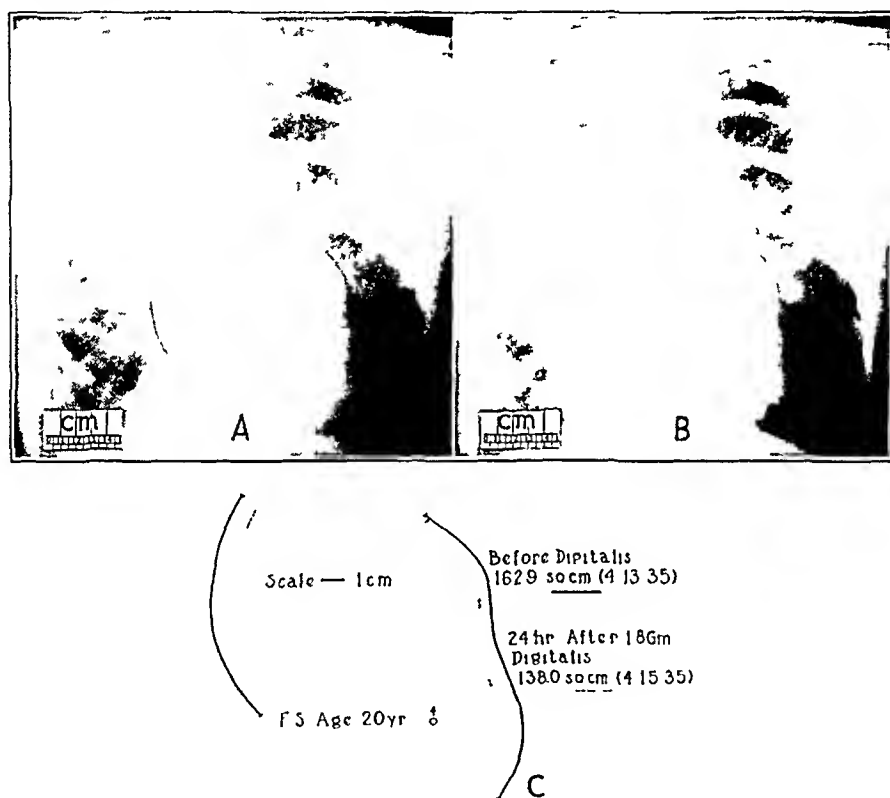


Fig 2 (case 1) —The change in the size of the heart after the administration of 1.8 Gm of digitalis. *A* was taken (April 13, 1935) before and *B* was taken (April 15) twenty-four hours after the administration of the drug. In *C* the outlines of the heart traced from *A* and *B* are superimposed.

per beat, a decrease in the size of the heart and a shortening of the circulation time (table 1 and figs 3 and 4). In this patient these trends were maintained with continuation of the drug. The results in 2 other patients suffering from rheumatic (cases 6 and 7) as well as 1 (case 16) suffering from arteriosclerotic heart disease followed a similar pattern (table 1).

Group 3 No Change in Cardiac Output Case 8 illustrates the effect of digitalis in this group of 6 patients (cases 8 to 13, table 1). The

giving of 18 Gm of digitalis to this patient was associated with no significant change in cardiac output, cardiac size, circulation time or venous pressure (table 1 and figs 5 and 6), although changes in the T wave of the electrocardiogram were recorded

II OBSERVATIONS RELATING TO PATIENTS EXHIBITING AURICULAR FIBRILLATION

The notion is current that the action of digitalis is not the same when auricular fibrillation is present as it is when regular sinus rhythm is

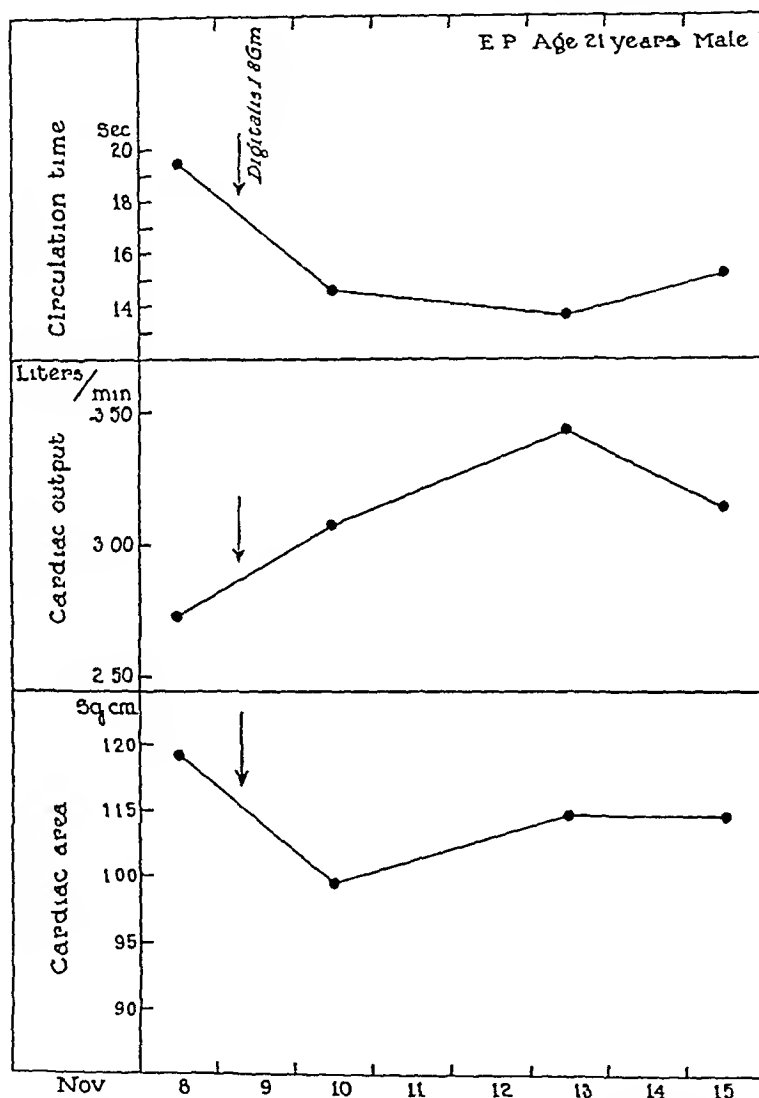


Fig 3 (case 5) —The effect of digitalis on the cardiac output, cardiac size and circulation time of E P, representing group 2

present Our earlier observations¹ indicated that the action of the drug is similar under these two conditions Our present observations were designed to yield additional data on this subject

Observations were made on 5 patients exhibiting auricular fibrillation who satisfied the following criteria (a) They suffered from

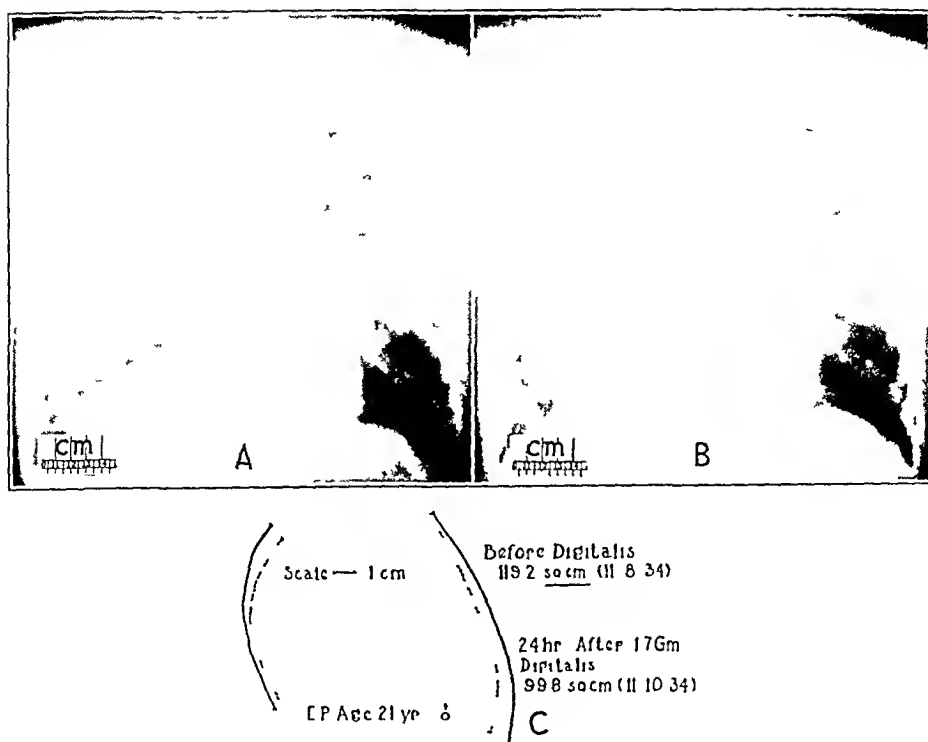


Fig 4 (case 5) —The change in the size of the heart *A* was taken (Nov 8, 1934) before and *B* (November 10) twenty-four hours after digitalis was given. In *C* the outlines of the heart traced from *A* and *B* are superimposed.

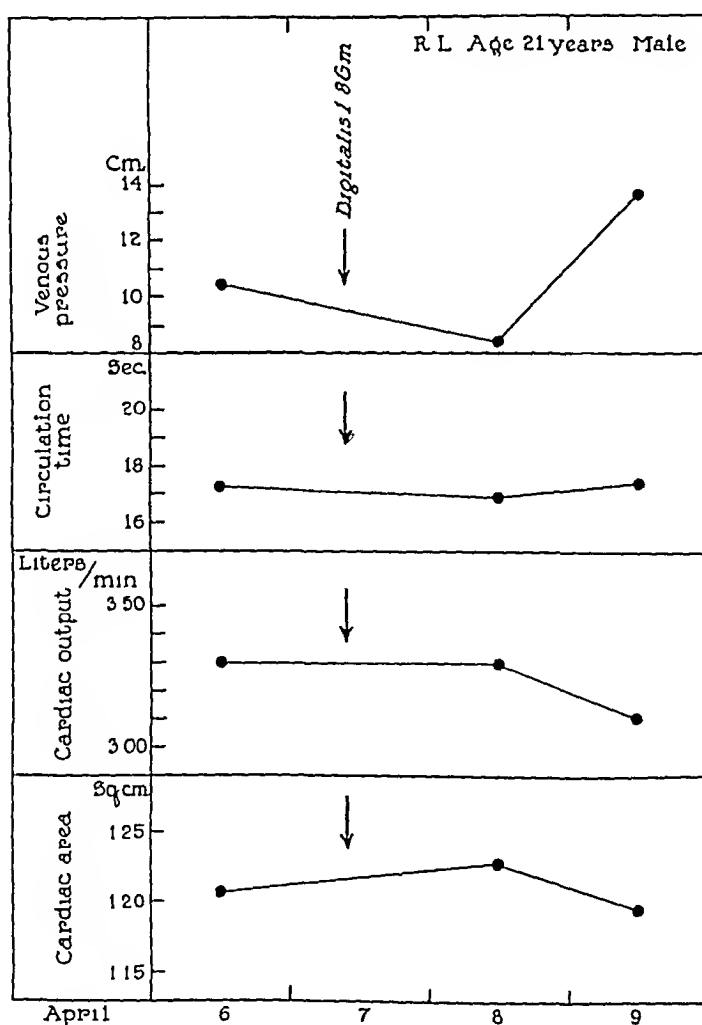


Fig 5 (case 8) —The effect of digitalis on the cardiac output, cardiac size, venous pressure and circulation time of R L, representing group 3.

organic heart disease, and (b) they did not exhibit signs of congestive heart failure at the time these observations were made. To each was given within twenty-four hours the same amount of digitalis (17 to 18 Gm) from the same batch as that given to the groups of patients with normal sinus rhythm as well as to those suffering from congestive heart failure^{2a}. The plan of the observations was similar to that already outlined in the section on methods.

Observations—Before digitalis was given the cardiac output of all the patients was less than the calculated normal output (table 2). In 3 cases (cases 18 to 20) the giving of digitalis in the manner described

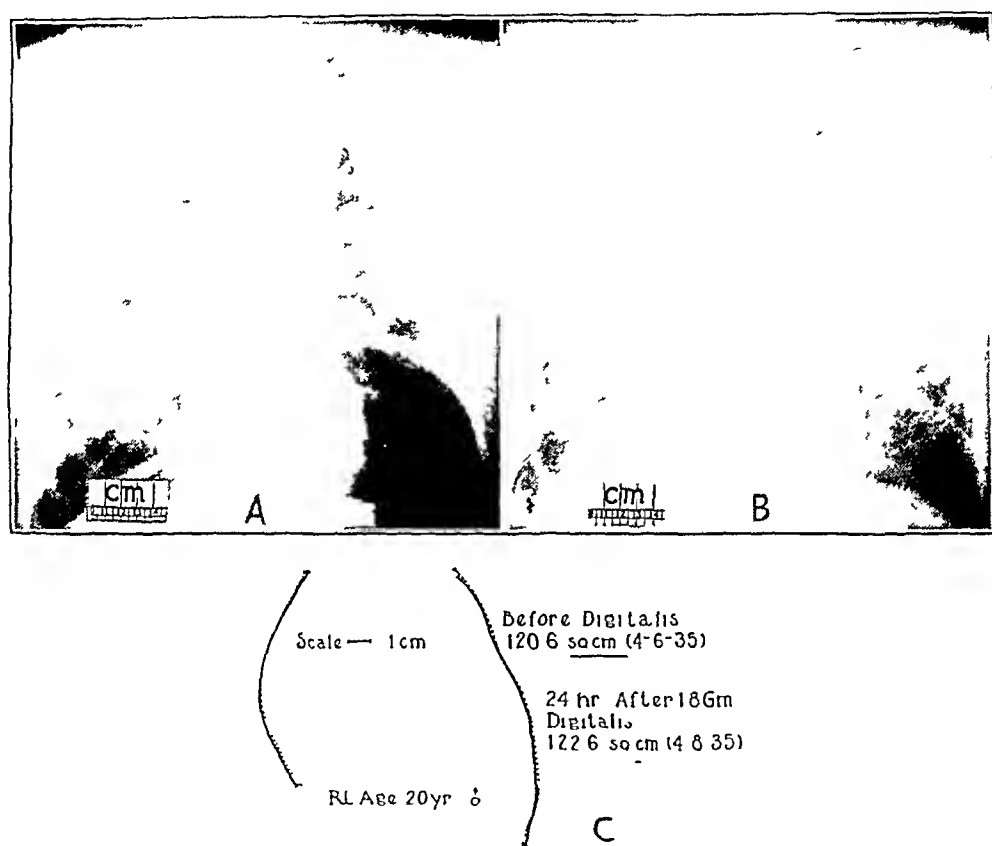


Fig 6 (case 8)—Roentgenograms of R L. *A* was taken (April 6, 1935) before and *B* (April 8) twenty-four hours after digitalis was given. In *C* the outlines of the heart traced from *A* and *B* are superimposed.

resulted in twenty-four hours in an increase in cardiac output per minute and per beat (table 2) and a decrease in the size of the heart. The circulation time was shortened in 1 case in which it was measured (case 20). No change in the venous pressure occurred in the 1 case in which it was recorded (case 18). In 2 other cases (cases 21 and 22, table 2) twenty-four hours after the drug was given the cardiac size was unchanged, and the cardiac output was unchanged, but the cardiac output per beat was increased. No significant changes in circulation time and venous pressure occurred.

COMMENT

The administration of digitalis in the same amounts to 13 patients with rheumatic heart disease for whom approximately the same functional classification could be made (group I or group II A) and the making of observations at the same time with respect to the giving of the drug showed an increase in output in certain cases, a decrease in others and no change in still others. We should be at a loss to account for these differences did we not have data relating to cardiac size, circulation time and venous pressure. One result of the action of digitalis appeared to be common to two groups, namely, a decrease in cardiac size, when the cardiac size decreased, the cardiac output altered, when the cardiac size remained unchanged, the cardiac output likewise remained unchanged. Furthermore, a decrease in cardiac size in certain instances was associated with a decrease in cardiac output and in others with an increase in cardiac output. Most of the patients showing a decrease in cardiac output showed slowing of the circulation time, just as most of those having an increase in cardiac output showed shortening of the circulation time, in short, acceleration of the blood flow. It is recalled that a decrease in cardiac output and in cardiac size has been observed (Stewart and Cohn) in normal human beings,¹ in normal dogs³ and in dogs having large hearts⁴ when digitalis has been given. Moreover, an increase in cardiac output and a decrease in cardiac size have been observed¹ and further confirmed by us^{2a} (Stewart, Deitrick, Crane, and Wheeler) in patients suffering from congestive heart failure. The effect of the size of the heart under the influence of digitalis on the volume of blood pumped by it is given added significance by the observation that when the cardiac size was unaltered the cardiac output was also unchanged. The effects, an increase or decrease in output, became less as the drug was excreted, or they remained approximately the same if its use was continued. Moreover, the few observations relating to other etiologic types indicates that the effects which have been described are not confined to cases of rheumatic heart disease. The effect on cardiac size appears at times to outweigh an effect on contraction which has been demonstrated in man and in dogs (Cohn and Stewart¹⁸). Though the extent of ventricular contraction might be increased the decrease in size was sufficient in some instances to make the output smaller.

These observations strengthen our notion that in normal persons as well as in the patients with cardiac disease now described, a decrease in cardiac output is a consequence of the fact that the heart has been made

18 Cohn, A. E., and Stewart, H. J. Evidence That Digitalis Influences Contraction of the Heart in Man, *J. Clin. Investigation* 1: 97 (Oct.) 1924, footnotes 3 and 4.

smaller by an action of the drug on it. It does not seem possible to attribute the decrease in output in these instances in man to diminished venous filling, a consequence of constriction of the hepatic veins (Dock and Tainter¹⁹), in the first place, a fall in venous pressure did not occur, in the second place, the decrease in venous pressure which Dock and Tainter observed in dogs was transient, a matter of minutes (under thirty minutes in most instances), but the effects we observed on size and output were present for a matter of days, in the third place, we were unable to observe a change in the size of the liver. It may be recalled that Tainter and Dock^{19b} showed that giving digitalis to dogs results, by its action on the hepatic veins, in an increase in the volume of the liver. The output of blood from the heart of 1 of our patients (case 4, table 1) decreased from 3.77 liters per minute to 2.98 liters per minute, twenty-four hours after 1.8 Gm of digitalis was given, in short, a falling off of one quarter of its minute volume. Nevertheless, the size of the liver in roentgenograms did not increase. When congestive heart failure supervened, two years later, the liver became swollen and tender, indicating that it was capable of distention. In none of these patients showing a decrease in output was there clinical evidence of enlargement of the liver after digitalization. Finally, in the fourth place, we may emphasize the argument made in an earlier paper (Stewart and Cohn¹) that constriction of the hepatic veins in man, even though their lumens were reduced to zero, would be insufficient to account for the magnitude of decrease in cardiac output which we have recorded.

If digitalis makes the heart a smaller pump and if it pumps a smaller amount of blood, the issue might be raised that the venous pressure should become elevated, in short, that the resulting situation would resemble the defect exhibited in chronic constrictive pericarditis. In the case of the latter, our own observations,²⁰ as well as those of Burwell and his associates,²¹ have shown interference not only with filling of the heart, since the heart in diastole is unable to stretch the

19 (a) Dock, W., and Tainter, M. L. Circulatory Changes After Full Therapeutic Doses of Digitalis, with a Critical Discussion of Views on Cardiac Output, *J Clin Investigation* 8:467 (April) 1930. (b) Tainter, M. L., and Dock, W. Further Observations on the Circulatory Actions of Digitalis and Strophanthus, with Special Reference to the Liver, and Comparisons with Histamine and Epinephrine, *ibid* 8:485 (June) 1930.

20 Stewart, H. J., and Heuer, G. J. Measurements of the Circulation in Constrictive Pericarditis Before and After Resection of the Pericardium, *Tr A Am Physicians* 52:342, 1937.

21 Burwell, C. S., and Strayhorn, W. D. Concretio Cordis. I. A Clinical Study with Observations on the Venous Pressure and Cardiac Output, *Arch Surg* 24:106 (Jan) 1932. Burwell, C. S., and Flickinger, D. Obstructing Pericarditis. Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis, *Arch Int Med* 56:250 (Aug) 1935.

fibrous sac, but also with emptying, since the heart cannot contract adequately That filling of the digitalized heart is not compromised and that it receives all the blood presented to it is shown by the absence of a rise in venous pressure In man piling up of blood on the venous side has not been observed as a consequence of giving digitalis What the distribution of the volume of circulating blood may be is not known

In this connection there remains to be considered the data reported by Rytand²² He observed the effect of digitalis on the venous pressure of human beings and came to the conclusion that a decrease in cardiac output was a consequence of a fall in venous pressure In the first place, not only were the changes which he observed in venous pressure sometimes above and sometimes below the initial level in the same patient, but they were of small magnitude They do not appear to us to be significant, for we have observed changes greater than these in the venous pressure from day to day in a normal person without medication under basal conditions²³ Even though a decrease had been a consistent finding, the slight change which he observed does not appear to be of sufficient magnitude to account for the marked change in cardiac output and in size which we have found In the second place, since he did not make observations on the cardiac output of his subjects, it is not possible to say what changes in cardiac output, if any, occurred Moreover, no observations were made of any other functions, such as those shown in electrocardiograms, by which to establish objectively one effect of digitalis with which to correlate the alteration in venous pressure And, finally, he has treated data from our observations¹ in a fashion which is open to question He plotted our figures for cardiac output against his figures for venous pressure and concluded that the decrease in cardiac output was due to a fall in venous pressure However, examination of our charts in which the raw data were plotted¹ showed that in not a single case was parallelism revealed between the decrease in cardiac output and cardiac size, on the one hand, and the decrease in venous pressure, on the other Obviously a relation which was not revealed in a single one of our cases cannot serve as a basis for arriving at the generalization he has made

There appears to be no reason for changing our original view that the decrease in cardiac output which we observed was associated with a decrease in the size of the heart Indeed, the data now recorded strengthen it

22 Rytand, D A The Effect of Digitalis on the Venous Pressure of Normal Individuals, *J Clin Investigation* **12** 847 (Sept) 1933

23 Stewart, H J, and Watson, R F Studies of the Circulation in Athletes, to be published

The effect of digitalis on the work of the left ventricle per beat was calculated. The opinion has been expressed (Stewart and Cohn²⁴) that the explanation of the increase in cardiac output with the decrease in cardiac size as a consequence of the giving of digitalis is to be found in Starling's²⁴ "law of the heart". Starr and his associates²⁵ have presented since then data indicating that this "law" applies to basal cardiac work in human beings as well as to that in the heart-lung preparation, since they found that the work of the left ventricle which is maintaining an adequate circulation bears a linear relation to the size of the heart. From their data they have defined a zone of normal circulatory function. In a manner similar to theirs we have plotted cardiac volumes as abscissas and gram meters of work of the left ventricle per beat as ordinates (table 1 and figs 7 and 8). The values for only 5 of the 17 patients with normal rhythm fell outside the zone of normal circulatory function, below line *CD*, in an area indicating that the work of the heart was not commensurate with its size. When these 5 were given digitalis, not all could be assigned to a single group (groups 1, 2 or 3), as might have been expected, but some belonged to each of the three groups indicated. A distinction so far as response to digitalis was concerned could not be made on this basis. In all the 5 cases mentioned, digitalis raised the values appreciably closer to or into the zone of normal circulatory function, whether the cardiac output was increased, decreased or unchanged by the drug. Moreover, in none of the 17 cases was the cardiac efficiency with the patient at rest diminished by the giving of digitalis, but the values moved closer to the best line of regression, *AB*. Though there were the three results with respect to cardiac output per minute, it appears that there is a common underlying effect of the drug in all these cases, namely, the work of the heart per beat was brought in all instances more in line with the work expected of it for its volume. Basis is thereby afforded Christian's recommendation of giving digitalis to patients exhibiting organic valvular disease before the occurrence of congestive heart failure.⁷ A decision as to whether or not digitalis is of "benefit" in the long run in such cases will depend on clinical observations regarding the life span and the state of well-being of a large series of patients during treatment as compared with observations on a group of untreated patients to whom the drug is not administered until congestive heart failure supervenes. After the giving of digitalis the visible and

24 Starling, E. H. The Linacre Lecture on the Law of the Heart, Given at Cambridge, 1915, London, Longmans, Green & Co., 1918.

25 Starr, I., Jr., Donal, J. S., Margolies, A., Shaw, R., Collins, L. H., and Gamble, C. J. Studies of the Heart and Circulation in Disease. Estimations of Basal Cardiac Output, Metabolism, Heart Size, and Blood Pressure in Two Hundred and Thirty-Five Subjects. *J. Clin. Investigation* **13**: 561 (July) 1934. Starr, Collins and Wood.¹⁶

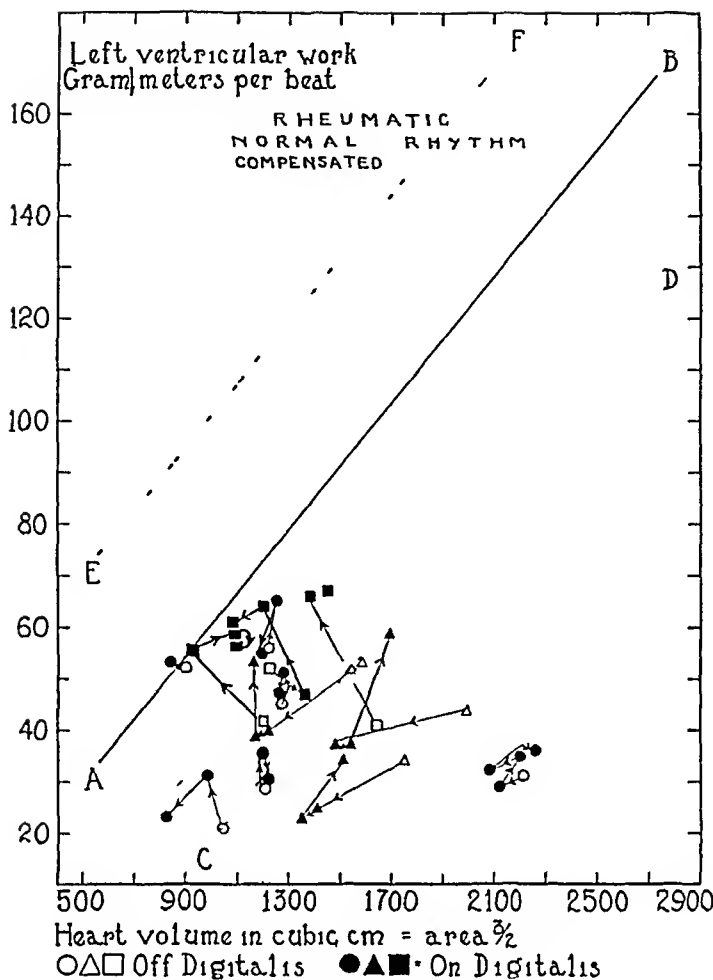


Fig 7—The work of the left ventricle per beat and the cardiac volume. The data from table 1 relating to the work of the left ventricle per beat in rheumatic heart disease particularly (cases 1 to 3 and 5 to 13) are plotted against the corresponding cardiac volumes. Line *AB* represents the best line, "the regression of the work on the area," defined by Starr, Collins and Wood¹⁶ (and illustrated in their figure 2) on the basis of a statistical treatment of data for a control group of patients. Lines *CD* and *EF* were placed by these authors at a distance of twice the standard deviation from *AB*. It appears from their observations that a patient whose values fall within zone *CD-EF* has a normal circulatory function, that is to say, the work of the heart is commensurate with its size, on the other hand, they found that the values relating to patients who had suffered from cardiac decompensation fell in a zone below *CD*. In our series, the values for all the patients except 1 (case 5, the data relating to case 4 were not plotted) fell in the zone representing normal circulatory function. The triangles represent patients whose cardiac output decreased (group 1), the squares, those whose output increased (group 2), and the circles, those whose output did not change (group 3) after the giving of digitalis. In this figure as well as in figures 8 and 9 open symbols indicate "before" and closed ones "after" the giving of digitalis. Arrows point from the first observations to those made later. All the observations made after digitalis was given are recorded by solid symbols, whether the use of the drug was continued after the digitalizing amount or not, since the amount of exertion could not be ascertained. The values for C W (case 4) were not plotted on the chart because they fell so far below line *CD* and to the right that it did not seem worth while to increase the dimensions of the chart in order to include him. In all instances the giving of digitalis made the values for the patient take up a more advantageous position on the chart.

the palpable apex thrust became more forceful, and on auscultation the heart appeared to be contracting more forcefully and emptying more completely

In the group of patients with auricular fibrillation the work of the left ventricle of the heart per beat was increased also in each instance by the giving of digitalis, so that the work came more nearly in line with

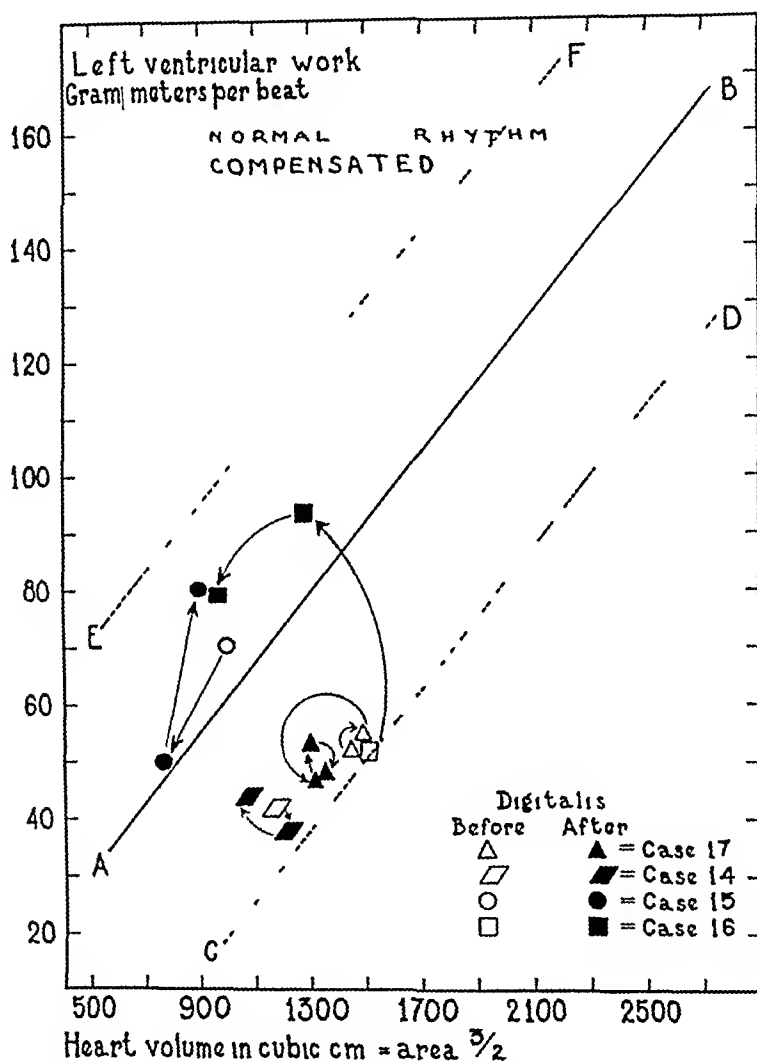


Fig 8—In this figure the work of the left ventricle per beat is plotted against the cardiac volume in cases 14 to 17, all the values fell in the zone of normal circulatory function, nevertheless, the giving of digitalis raised each to a more advantageous position

that expected of the heart for its size. The values for 3 patients (cases 20 to 22) in this group moved up into the zone of normal circulatory function, *CD-EF*, during rest (fig 9), and those for 2 others (cases 18 and 19) moved nearer the best line, *AB*.

We have seen that the results of giving digitalis to patients suffering from compensated heart disease are not predictable, for in some cases the heart behaved like a normal heart, a decrease in the size of the

pump being associated with a decrease in the output, and in other cases it behaved like the dilated heart of a patient suffering from heart failure, restoration of the cardiac size to a more optimal level resulting in an increase in output¹ The functional state of the heart in these cases could not be distinguished clinically Moreover, there were no similar features for each group so far as concerned the level of cardiac output, cardiac size or circulation time before digitalis was given, which made them fall later into these groups, nor did they fall together with respect to the work of the heart Group 3 is puzzling, for it may be recalled

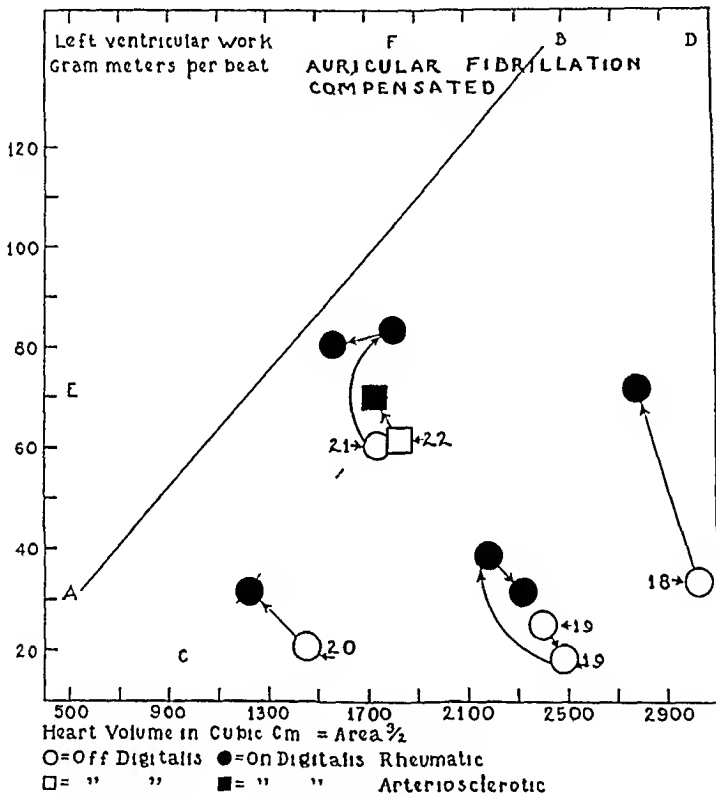


Fig 9—In this figure the work of the left ventricle per beat is plotted against the cardiac volume in cases 18 to 22, cases in which there was auricular fibrillation, after digitalis was given the values for 3 moved up into the zone of normal circulatory function, and those for the other 2 moved closer to the line CD

that giving digitalis to these patients did not alter the cardiac output per minute, nor did it alter the cardiac size, circulation time or venous pressure Nevertheless, a digitalis effect was present for the T wave of the electrocardiogram showed characteristic changes²⁶ Various factors

26 Cattell, McK, and Gold, H The Influence of Digitalis Glucosides on the Forces of Contraction of the Mammalian Cardiac Muscle, *J Pharmacol & Exper Therap* 62 116 (Jan) 1938

about which we have no data must have neutralized each other so that a change in size and output did not occur. This group 3 exhibited in a fashion similar to that exhibited by the other two increase in the work of the heart per beat. Although the observations were confined largely to subjects with rheumatic heart disease, the few observations made on subjects with other etiologic types of heart disease showed that the phenomena described are not confined to the category of rheumatic heart disease.

Furthermore, observations on the patients exhibiting auricular fibrillation showed that the effect of the action of digitalis on them was not different from the effect on those exhibiting a normal sinus mechanism. Those having an increase in output after digitalization were found to show a decrease in the size of the heart, and those having no change in output showed no significant change in the size of the heart, observations which parallel those made for patients with normal sinus rhythm. Once again it is demonstrated that the effect on the size of the heart is pertinent. Though the cardiac output per minute in 2 cases was unchanged, the output per beat was increased, owing in part to slowing of the heart rate and in part probably to an increase in ventricular contraction.¹⁸ As we have already pointed out, the phenomenon common to all groups—whether the output was increased, decreased or unchanged and whether the rhythm was regular or that of auricular fibrillation—was that the work of the heart per beat was made commensurate (or more nearly so) with its size.

The bearing on this subject of the recent observations of Cattell and Gold²⁶ relating to the effect of digitalis on systolic tension is discussed in our paper dealing with uncompensated heart disease.^{2a}

SUMMARY

We gave 1.6 to 1.8 Gm of digitalis within twenty-four hours to 13 patients suffering from rheumatic heart disease and to 4 others with arteriosclerotic, hypertensive or syphilitic heart disease. In all cases there was compensation, and a normal sinus mechanism was exhibited. In addition to clinical studies of these patients, special observations were made of the cardiac output, cardiac size, circulation time and venous pressure. In all cases the T wave and the R-T segment of the electrocardiogram showed the changes characteristic of a digitalis effect. It was found that 7 patients showed a decrease in cardiac output and a decrease in cardiac size, 4 patients showed an increase in cardiac output and a decrease in cardiac size and 6 patients showed no change in cardiac output and in cardiac size. In short, in some instances when the heart was made smaller, the cardiac output increased, and in others it decreased. In the former cases the heart behaved like a failing heart (part II of

our previous study ¹)^{2a} and in the latter cases like a normal one (part I of our previous study ¹) We were unable to predict beforehand which effect would be produced

The results in 5 patients exhibiting auricular fibrillation were not different from those encountered in those with normal sinus rhythm—a decrease in cardiac size was associated with a decrease in cardiac output, and an unchanged cardiac size was associated with an unchanged cardiac output

Digitalis has four effects on the heart which may be recorded clinically (1) an effect on contraction,¹⁸ namely, an increase, (2) an effect on size (Stewart and Cohn ²⁷ and observations in this paper), namely, a decrease, (3) an effect on the cardiac rate, namely, a decrease,¹ and (4) an effect on the electrocardiogram,²⁸ indicating an effect on the cardiac muscle The cardiac output which results is different, depending on the individual heart, that is to say, whether it is dilated or not

A few observations on patients with heart disease due to other etiological factors showed that these phenomena are not confined to those with rheumatic involvement

There is one phenomenon which is common to all groups The giving of digitalis increases the work accomplished by the heart per beat, whether its action is to increase or to decrease the output or to leave it unaltered and whether the rhythm is regular or that of auricular fibrillation As a consequence, work becomes more nearly appropriate for the size of the organ Some basis is afforded Christian's suggestion of giving digitalis to the patient suffering from organic heart disease even though he shows no significant failure

These studies yield additional evidence that a decrease in cardiac output which follows the giving of digitalis to human beings (normal and those having organic heart disease without congestive heart failure) is not a consequence of diminished venous return but a consequence, so far as we can now ascertain, of a decrease in the size of the heart due to the action of digitalis on it

27 Stewart and Cohn ¹ Cohn and Stewart ^{3,4}

28 Stewart, H J, and Watson, R F The Effect of Digitalis on the Form of the Human Electrocardiogram, with Special Reference to Changes Occurring in the Chest Lead, *Am Heart J*, to be published

ACTION OF DIGITALIS IN UNCOMPENSATED HEART DISEASE

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It has been demonstrated as a fact that digitalis decreases the cardiac output (Stewart and Cohn¹ and Burwell, Neighbors and Regen²) and the cardiac size in normal human beings (Stewart and Cohn¹) It was found (Stewart and Cohn¹) that the cardiac output was diminished and the heart dilated in the presence of congestive heart failure and that the administration of digitalis in these instances increased the cardiac output and decreased the cardiac size We (Stewart, Crane, Deitrick and Thompson³) have recently published data relating to patients suffering from organic heart disease, without congestive heart failure, with normal rhythm In certain of these cases the behavior of the heart was normal, in others the behavior was like that of a failing heart In addition, we³ have shown in these later observations that digitalis increased the work of the heart per beat Moreover, the action of the drug was the same whether the rhythm was that of a normal sinus mechanism or of auricular fibrillation³

In rounding out our study of the action of digitalis we wished to investigate further its action in the presence of congestive heart failure when a normal sinus mechanism was exhibited as well as when auricular

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An abstract of these studies was presented before the American Heart Association, Kansas City, Kan, May 12, 1936

1 Stewart, H J, and Cohn, A E III Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart, *J Clin Investigation* **11**:917 (Sept) 1932

2 Burwell, C S, Neighbors, DeW, and Regen, E M The Effect of Digitalis upon the Output of the Heart in Normal Man, *J Clin Investigation* **5** 125 (Dec) 1927

3 Stewart, H J, Crane, N F, Deitrick, J E, and Thompson, W P Action of Digitalis in Compensated Heart Disease, *Arch Int Med*, this issue, p 547

fibrillation was present, since there are still differences of opinion as to the action of the drug in the presence of a failing heart. These data form the basis of this paper.

I OBSERVATIONS ON PATIENTS EXHIBITING NORMAL SINUS RHYTHM

Plan of Observations—In order to make our observation comparable not only within this group but also with respect to the observations on the other groups studied,³ we maintained the following uniform conditions:

(a) All the patients were at rest in bed during the period of these observations, (b) all observations were made in the morning while the patients were in a basal metabolic state, (c) all the patients exhibited a regular sinus mechanism, (d) all the patients were given the same amount of the drug,⁴ namely, 1.7 to 1.8 Gm, within twenty-four hours, distributed in the same fashion, the digitalis was of the same "batch" as that used in the former observations,³ (e) studies were made the day before and again twenty-four hours after the giving of digitalis and then again at varying intervals later. We adhered to making observations twenty-four hours after giving the drug because our observations have shown that the early effects of digitalis are important. In those instances in which the use of digitalis was continued, the observations were made as usual in the morning, and the maintenance dose of the drug was given later in the day. All the patients were given the diet prepared for patients in the wards, containing 2 Gm of salt. The intake of fluid was fixed. The methods and order of making observations were recorded in our first paper.³ In the technic of rebreathing for estimation of the arteriovenous oxygen difference, the amount of gas in the "rebreathing bag" was adjusted to the amount which, as had been found by trial beforehand, the patient could take completely.

Observations—Observations were made on 11 patients. In 6 of these cases the etiologic diagnosis was hypertension (cases 1 to 6, inclusive), in 2 rheumatic fever (cases 7 and 8), in 1 syphilis (case 9), in 1 arteriosclerosis (case 10) and in 1 tuberculosis, giving rise to chronic constrictive pericarditis (case 11). All the patients exhibited signs and symptoms of congestive heart failure.

The case of A. F. (case 1) illustrates the effect of giving digitalis in the presence of congestive heart failure as a consequence of hypertension. During failure the cardiac output was diminished, the heart large, the circulation time prolonged and the venous pressure elevated (table 1). The patient was so ill that treatment with digitalis was started immediately after these observations were recorded, and digitalization was continued into the following day; he received the digitalizing amount, 1.8 Gm in twenty-four hours, and the maintenance amount for the second day. The administration of 2.1 Gm of digitalis in thirty-six hours resulted in an increase in the cardiac output per minute (table 1 and fig. 1) and per beat, a decrease in the cardiac size, a shortening of the circulation time, a lowering of the venous pressure and an increase in

4 See the tables for exceptions.

vital capacity With the continued use of digitalis these relations were maintained, the heart, however, becoming still smaller The patient's condition improved, and he became free from the signs and symptoms of heart failure

The data for a second patient (E R) in this group (case 4, table 1) illustrate the effect of the drug in the presence of paroxysmal nocturnal dyspnea The patient was being given 3 Gm of theobromine with sodium salicylate daily, and this was kept constant during the period of the observations The giving of 1.8 Gm of digitalis to this patient resulted in twenty-four hours in an increase in cardiac output (fig 2), a decrease in cardiac size (figs 2 and 3), a shortening of the circulation time and no significant change in the venous pressure, which was not elevated The patient began sleeping better at once

The data for S S (case 7) illustrate the effect of giving digitalis in the presence of rheumatic heart disease (table 1) After 1.7 Gm of the drug was given, the cardiac output increased (table 1 and fig 4), the cardiac size decreased (figs 4 and 5), the circulation time decreased and the venous pressure fell The patient became free from the signs and symptoms of congestive heart failure

The data for J K (case 9) illustrate the effect of giving digitalis in the presence of syphilitic heart disease (table 1) The administration of 1.8 Gm of the drug in twenty-four hours resulted in an increase in cardiac output, a decrease in cardiac size, a shortening of the circulation time and a fall in the venous pressure (fig 6)

The case of C K (case 10) illustrates the effect of giving digitalis in the presence of arteriosclerotic heart disease (table 1) The patient was under the influence of digitalis when the first observations were made, on Oct 25, 1935 (fig 7) The use of digitalis was discontinued, and in the next sixteen days signs of congestive heart failure recurred and the patient gained weight At this time, on November 13, the heart had dilated from 155.3 to 176.2 sq cm, the cardiac output had decreased from 3.13 to 2.38 liters per minute, the circulation time had increased from twenty-two and seven tenths to thirty seconds and the venous pressure had risen from 9.4 to 19 cm On November 14, 1.8 Gm of digitalis was given On November 15 the cardiac output had increased to 2.8 liters per minute, the size of the heart had decreased to 164.3 sq cm, the circulation time had fallen to twenty and eight-tenths seconds and the venous pressure had fallen to 11.4 cm There were diuresis and a loss of weight

The effect of the drug after the resection of part of the pericardium of a patient suffering from chronic constrictive pericarditis is shown in case 11 (table 1) This patient, also, showed an increase in cardiac output and a fall in venous pressure The cardiac area was not measured, because of the presence of fluid in the right pleural cavity

TABLE 1—Data Relating to the Effect of Digitals in Eleven Cases

Case	Age	Sex	Date	Body Surface, Sq M	Oxygen Consumption, Cc per Min	Arterio-venous Oxygen Difference, Cc	Cardiac Output, L per Min	Cardiac Output, L per Sq M per Min	Cardiac Area, Sq Cm	Cardiac Volume, Cc *	Arterial Pressure, Mm Hg	Circulation Time, Sec
Hypertensive Heart Disease												
1 A F	38	M	1/ 4/36 1/4 5 36 1/ 6/36 1/ 8/36 1/15/36	1.62 1.57 1.54 1.55	286 249 205 203	110.9 66.6 68.9 59.6	2.58 3.74 3.00 3.41	1.59 2.38 1.95 2.20	167.2 147.6 137.3 123.3	1,970 1,634 1,466 1,326	211/145 204/108 192/132 205/128	22.3 15.3 16.4 12.5
2 M R	68	M	1/21/36 1/22/36 1/23/36 1/29/36	1.83 1.82 1.79	274 273 207	117.6 83.0 68.0	2.33 3.29 3.04	1.27 1.80 1.70	172.3 157.9 150.8	2,059 1,805 1,685	170/ 94 174/108 170/ 80	25.9 21.4 19.2
3 M H	73	M	11/23/35 11/24/35 11/25/35 11/27/35 12/ 3/35 12/11/35	1.71 1.70 1.70 1.68 1.69	280 241 216 230 220	98.3 79.7 71.9 68.9 70.9	2.85 3.03 3.00 3.34 3.10	1.66 1.80 1.80 2.00 1.84	218.2 196.8 197.7 196.0 196.7	2,935 2,515 2,532 2,500 2,512	153/110 162/110 160/102 148/ 98 148/ 95	35.1 26.1 30.6 29.1 29.0
4 E R	44	M	5/11/35 5/12/35 5/13/35 5/15/35	1.78 1.77 1.77	265 251 232	77.9 66.6 65.3	3.40 3.80 3.60	1.91 2.15 2.00	212.3 184.2 178.4	2,822 2,280 2,172	150/108 166/110 158/110	30.0 23.0 26.2
5 F G	51	M	3/ 5/36 3/ 6/36 3/ 7/36 3/ 9/36	2.00 1.99 1.94	263 263 265	81.4 72.8 73.4	3.23 3.61 3.61	1.62 1.82 1.86	234.2 215.0 207.1	3,263 2,875 2,717	160/110 190/ 94 160/108	50.0 42.0 46.4
6 L B	64	M	2/29/36 2/29 3/ 1/36 3/ 2/36 3/ 6/36	1.77 1.76 1.73	249 218 216	82.8 63.7 59.2	3.01 3.42 3.65	1.70 1.94 2.11	141.1 133.6 125.9	1,526 1,435 1,287	200/114 212/108 212/100	15.8 16.0 16.4
Rheumatic Heart Disease												
7 S S	32	M	2/19/36 2/20/36 2/22/36 2/24/36	1.73 1.71 1.68	245 238 236	115.3 78.1 74.3	2.13 3.05 3.20	1.23 1.80 1.90	215.6 193.0 172.9	2,882 2,441 2,070	114/ 76 115/ 64 105/ 68	42.6 31.4 31.7
8 W B	32	F	4/28/36 4/29/36 4/30/36 5/ 2/36 5/ 7/36	1.48 1.48 1.46 1.39	207 201 205 166	106.3 85.2 84.0 82.3	1.95 2.36 2.44 2.02	1.32 1.59 1.67 1.50	194.2 170.0 175.4 183.4	2,448 2,020 2,118 2,260	110/ 80 122/ 80 116/ 72 98/ 65	27.0 23.4 27.0 24.0
Syphilitic Heart Disease												
9 J K	55	M	4/15/36 4/16/36 4/17/36	1.65 1.64	220 220	107.5 80.9	2.05 2.72	1.26 1.66	204.5 175.9	2,680 2,107	156/ 40 156/ 40	25.8 22.0
Arteriosclerotic Heart Disease												
10 C K	46	M	10/25/35 11/13/35 11/14/35 11/15/35 11/18/35 11/21/35	1.55 1.59 1.58 1.57 1.53	218 212 212 207 209	69.6 88.9 74.4 72.8 73.9	3.13 2.38 2.85 2.84 2.83	2.02 1.50 1.80 1.81 1.85	155.3 176.2 164.3 160.4 172.1	1,772 2,133 1,905 1,833 2,060	106/ 74 97/ 78 116/ 50 106/ 58 104/ 80	22.7 30.0 20.8 30.4 28.0
Chronic Constrictive Pericarditis after Pericardial Resection (Jan 28, 1936)												
11 A R	30	F	2/13/36 2/14/36 2/15/36 2/18/36	1.44 1.42 1.44	186 184 184	85.0 66.7 73.5	2.19 2.76 2.65	1.52 1.94 1.84	152 Could not be measured (fluid in chest)	100/ 75 96/ 64 105/ 75	10.9 10.2 9.9	

* The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text

† + and 0 indicate, in this table as well as in table 2, that diuresis did or did not take place

§ In this table, as well as in table 2, Hypt indicates hypertension, Enl Ht, enlarged heart, Artscel, arteriosclerosis, R I V HB, right intraventricular heart block, Rheu fever, rheumatic fever, M S, M I and A I, mitral stenosis, mitral insufficiency and aortic insufficiency, respectively, The, tuberculosis. The diagnoses in this paper conform to those recommended by the New York Tuberculosis and Health Association

§ In this table as well as in table 2, 0 indicates not present, +, present, ↓, decreasing, ↑, increasing ±, doubtful

of Uncompensated Heart Disease Associated with Normal Rhythm

Venous Pres- sure, Cm	Vital Capacity, Cc	Car- diac Rate, per Min	Car- diac Output, Cc per Beat	Work of Left Ven- tricle, Gm M per Beat	Digi- tals, Gm	Diuresis†	Diagnosis‡	Signs of Failures§					Fluid in Chest	Red Blood Cell Count and Hemo- globin Value¶	
								Cya- nosis	Liver	Rales	Edema	Dysp- nea			
Hypertensive Heart Disease															
21 0	1,400	94	29	76		—	Hvpt, Enl Ht	0	+	+	0	+	0	3 9 82	
6 6	1,900	76	49	94	2 1			0	↓	0	0	0	0		
7 8	2,100	76	40	88	0 2 q d			0	↓	0	0	0	0		
8 5	2,450	70	49	111	0 2 q d			0	±	0	0	0	0		
21 3	1,600	120	20	36		0	Artscl., Enl Ht, Hvpt	±	+	+	+	—	0	4 1 92	
13 8	2,300	94	35	67	1 5#			±	±	↓	0	±	0		
7 9	2,800	60	50	85	0 1 q d			0	0	0	0	0	0		
10 7	1,900	82	35	63		Slight	Artscl., Hvpt, Enl Ht, R-I-V HB	+	+	+	0	+	+	4 0 94	
7 2	2,300	64	47	87	1 8			↓	↓	↓	0	0	↓		
7 6	2,600	68	44	78	0 2 q d			0	↓	±	0	0	±		
6 4	2,850	64	52	87	0 2 q d			0	↓	0	0	0	0		
7 0	2,950	60	52	86	0 2 q d			0	↓	0	0	0	0		
8 4	3,400	98	35	61		0 ?	Hvpt Enl Ht	+	0	+	0	+	0	4 9 90	
6 9	3,750	80	48	90	1 8#			0	0	0	0	0	0		
7 9	3,900	80	45	82	0 2 on May 14			0	0	0	0	0	0		
21 5	2,700	68	47	86		+	Hvpt, Enl Ht	+	+	+	—	±	0	5 7 104	
12 3	2,800	66	55	106	1 8			↓	↓	↓	↓	↓	0		
13 3	2,900	58	62	113				↓	↓	±	0	±	0		
18 6	1,300	100	30	66		Lost weight	Artscl., Hvpt, Enl Ht	+	+	+	±	+	0	4 5 80	
4 3	1,800	74	46	100	2 2			↓	±	+	±	↓	0		
5 0	1,900	66	55	116	0 2 q d			0	0	+	0	±	0		
Rheumatic Heart Disease															
18 1	3,200	70	30	39		+	Rheu fever, MS, MI, Enl Ht	+	+	+	0	0	0	4 9 100	
9 7	3,400	54	56	69	1 7			0	↓	0	0	0	0		
5 8	3,450	58	55	61	0 2 q d			0	?	0	0	0	0		
17 0	1,500	80	24	31		Lost weight	Rheu fever, MS, MI, Enl Ht	+	+	+	+	—	±	108	
11 0	1,500	80	30	41	1 8			↓	↓	↓	↓	↓	±		
11 2	1,500	72	34	46	0 2 q d			0	?	↓	↓	0	0		
5 3	2,100	48	42	47	0 2 q d			0	0	0	0	0	0		
Syphilitic Heart Disease															
18 3	1,500	93	21	28		Slight	Syphilis A I, Enl Ht	+	+	+	+	—	+	4 9	
10 5	1,100	116	23	31	1 8			±	+	+	+	↓	↓		
Arteriosclerotic Heart Disease															
9 4	2,900	112	28	34	+	+	Artscl Enl Ht	±	+	0	0	0	0	4 5	
19 0	2,300	114	21	25	+			+	↑	0	+	+	0	74	
11 4	2,250	100	29	34	1 8			0	0	0	0	0	0		
8 7	2,800	100	28	32	0 2 q d			0	±	0	0	0	0		
9 4	3,050	96	30	37				0	±	0	0	0	0		
Chronic Constrictive Pericarditis after Pericardial Resection (Jan 28 1936)															
27 8	1,000	110	20	24		+	Tbc, chronic constrictive pericarditis	±	+	+	0	0	±	3 9 77	
22 7	900	96	29	32	1 8			0	±	+	0	0	±		
22 0	950	84	32	39	0 2 q d			±	±	+	0	0	±		

†† The values for red blood cells are given in millions, those for hemoglobin are given in percentages, 14.5 Gm of hemoglobin being equivalent to 100 per cent.

‡ When the patient was kept under the influence of digitalis, the measurements were made as usual in the morning, and the maintenance dose of digitalis was given later in the day.

This patient received 1 Gm of theobromine with sodium salicylate three times a day, from April 23, 1935. The dosage was not changed during the period of these observations.

** This patient received 1.5 Gm of a mixture of calcium theobromine and calcium salicylate three times a day. The dosage was continued unchanged throughout the period of these observations. The patient was under the influence of digitalis at this time, but its use was discontinued after the observations were made.

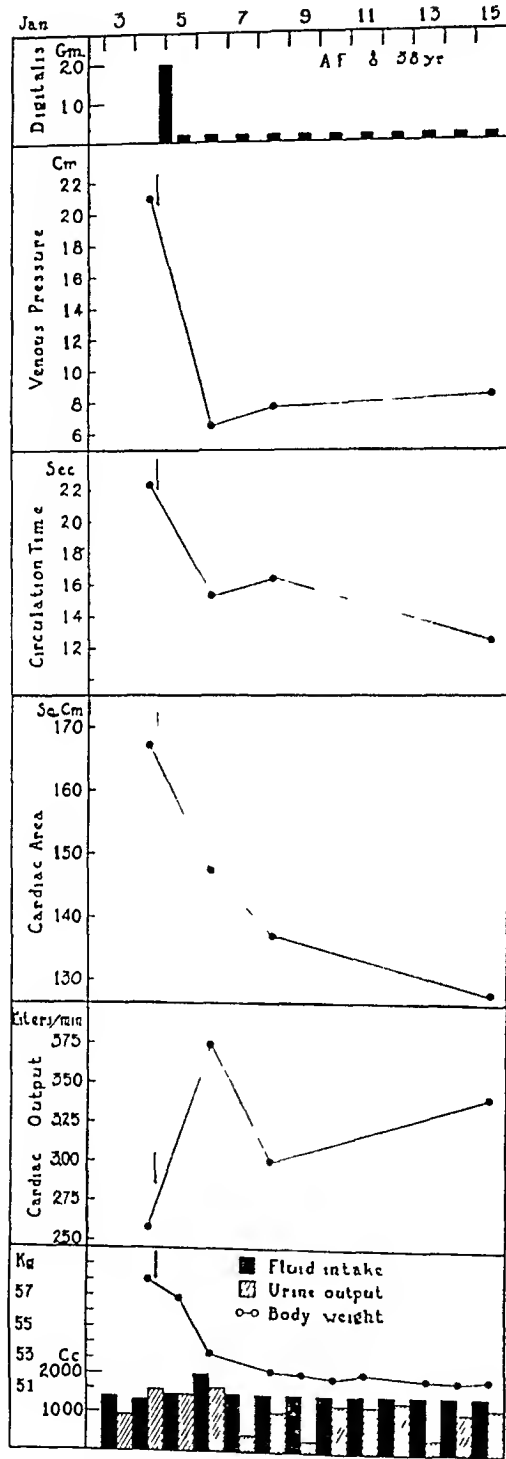


Fig 1—The effect of digitalis on urinary output and body weight, cardiac output, cardiac size, circulation time and venous pressure in case 1 in the presence of hypertensive heart disease. This patient, as well as those whose data are given in figures 2 to 7, inclusive, showed a normal sinus rhythm.

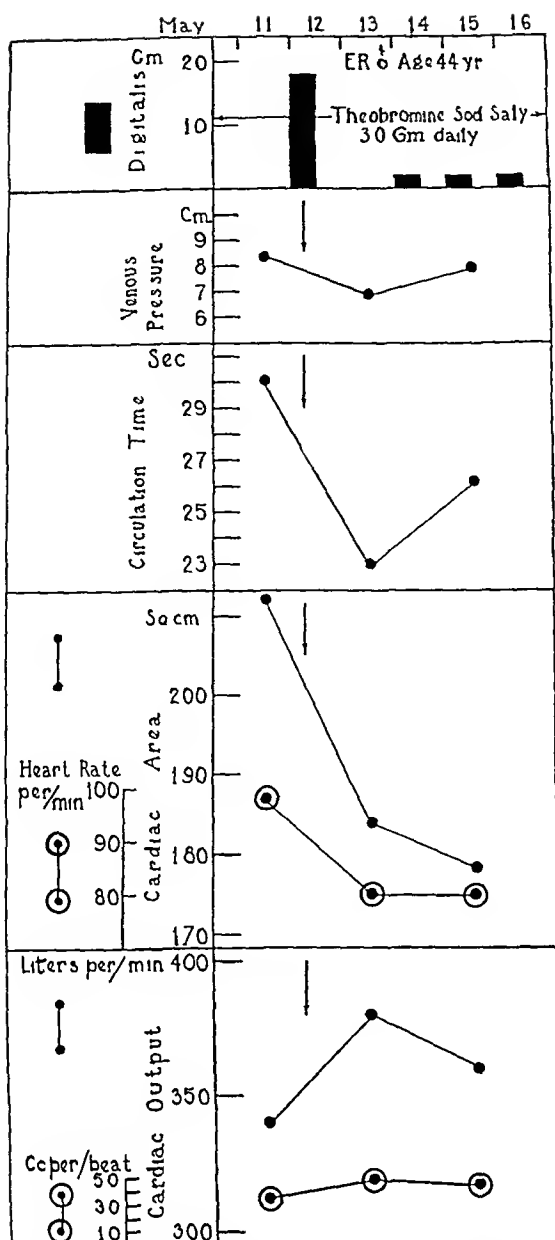


Fig 2—The effect of digitalis on the cardiac output per beat and per minute, heart rate, cardiac size, circulation time and venous pressure in case 4 (hypertensive heart disease) at a time when the predominant symptom was paroxysmal nocturnal dyspnea

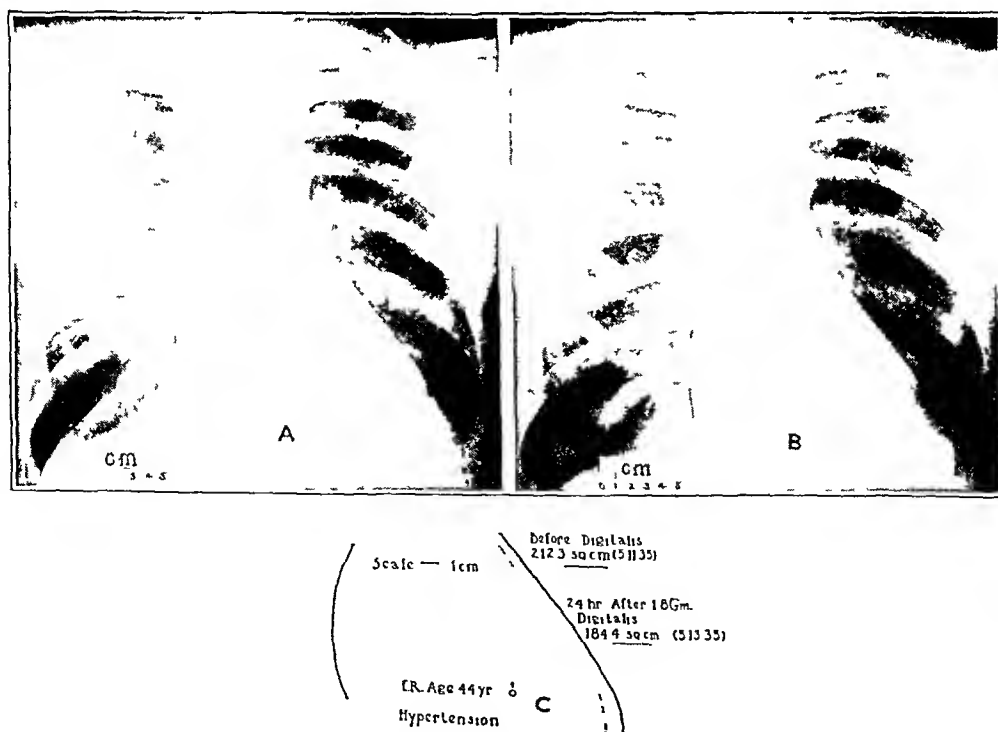


Fig 3—The change in the size of the heart after the administration of 18 Gm of digitalis in case 4. *A* was taken (May 11, 1935) before and *B* was taken (May 13) twenty-four hours after the administration of the drug. In *C* are shown superimposed the outlines of the heart obtained from tracings of *A* and *B*

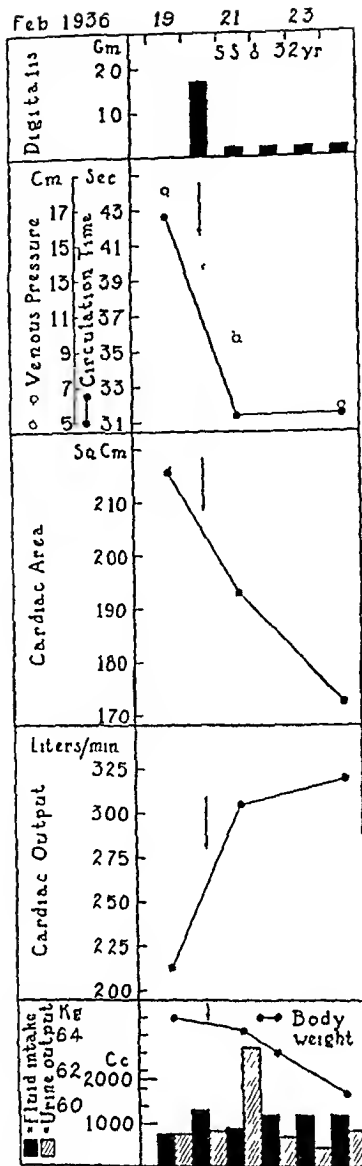


Fig 4—The effect of digitalis on the urinary output and body weight, cardiac output, cardiac size, venous pressure and circulation time in case 7 (rheumatic heart disease)

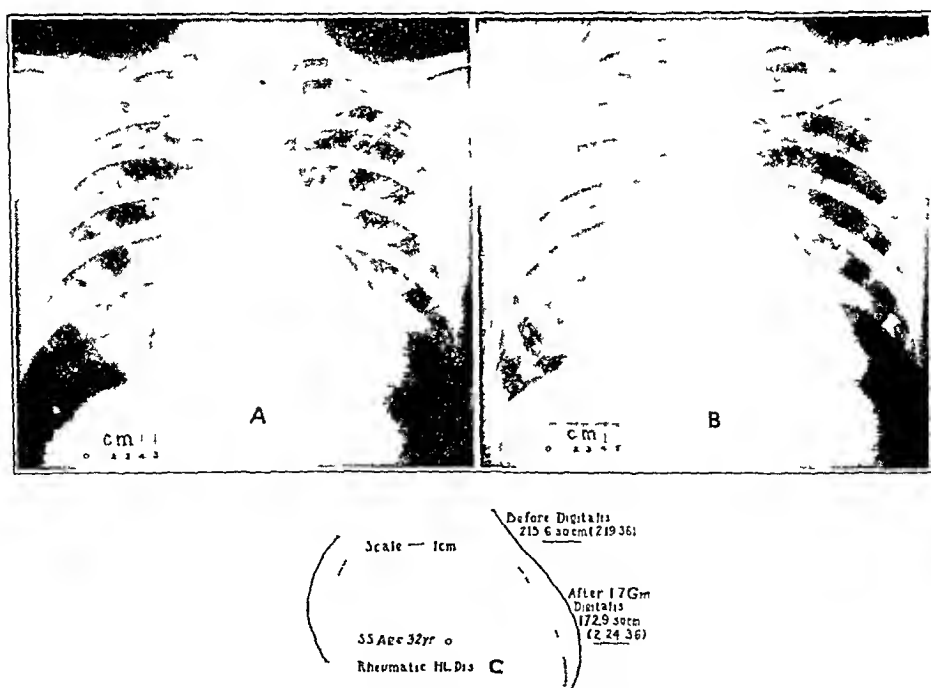


Fig 5—The change in the size of the heart after the administration of 17 Gm of digitalis in case 7. *A* was taken (Feb 19, 1936) before and *B* (February 24) three days after the administration of the drug. In *C* are shown superimposed the outlines of the heart obtained from tracings of *A* and *B*.

II OBSERVATIONS ON PATIENTS EXHIBITING AURICULAR FIBRILLATION

Plan of Observations—Observations were made on 9 patients with auricular fibrillation. In 7 cases the etiologic factor was rheumatic fever,

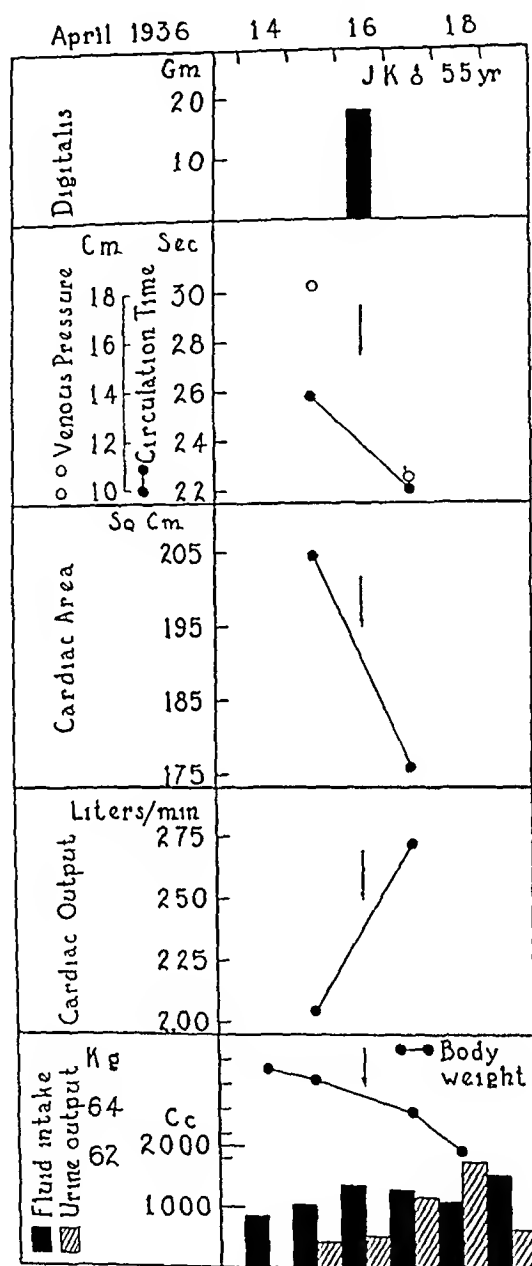


Fig 6—The effect of digitalis on urinary output and body weight, cardiac output, cardiac size, venous pressure and circulation time in case 9 (syphilitic heart disease)

in 1 syphilis and in 1 arteriosclerosis. In all there was evidence of congestive heart failure. The amount of the drug and the plan of procedure were similar to those followed in the cases of normal sinus rhythm.

Observations—The results secured in the case of J G (case 12) serve to illustrate the course of events in a patient with elevation of the

venous pressure (cases 12, 15, 19 and 20, table 2) Giving digitalis to this patient (1.8 Gm in twenty-four hours) resulted within twenty-four hours in an increase in cardiac output, a decrease in cardiac size

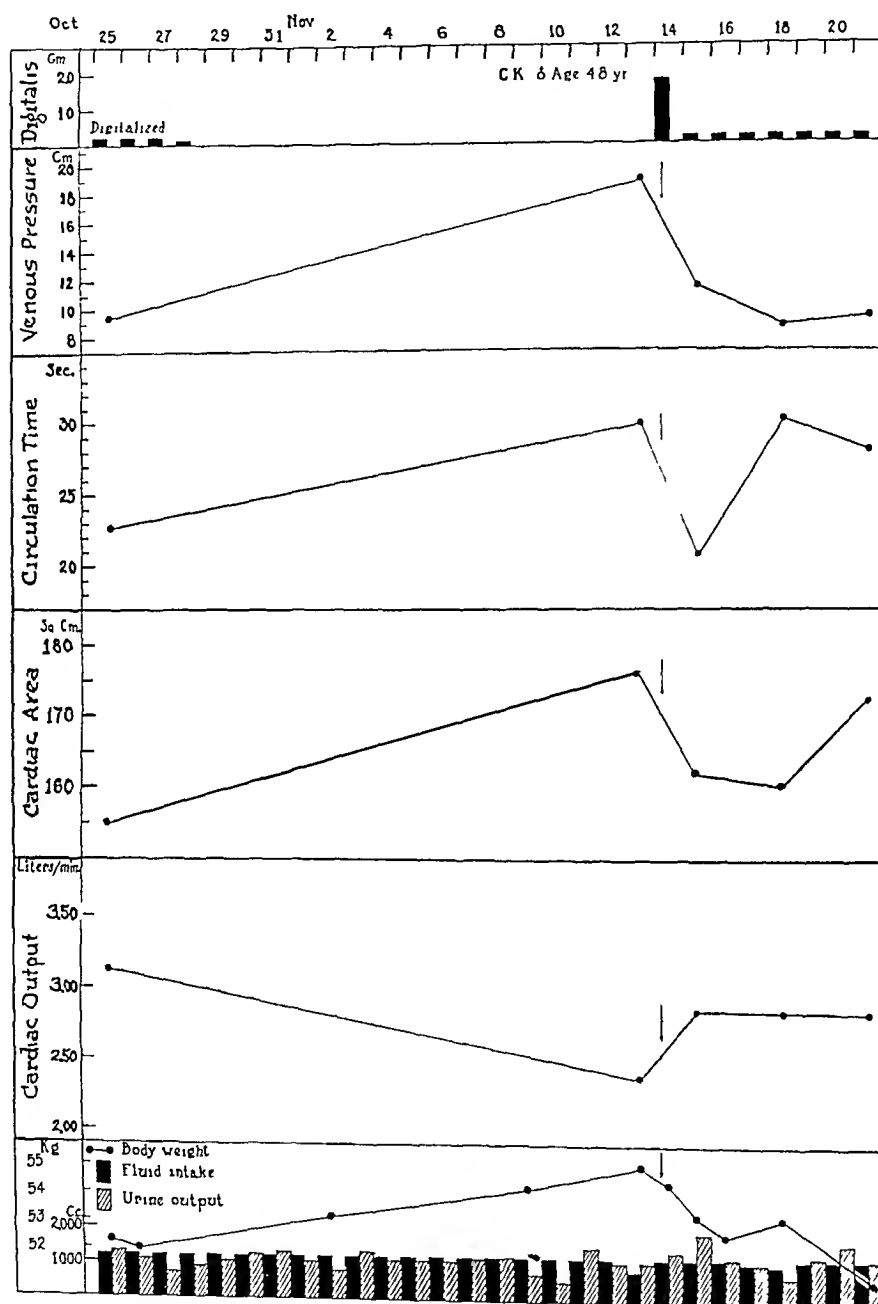


Fig 7—The effect of digitalis on urinary output and body weight, cardiac output, cardiac size, circulation time and venous pressure in case 10 (arteriosclerotic heart disease)

(fig 8), a shortening of circulation time and a fall in venous pressure. There was a fall in ventricular rate from 102 to 52 per minute, and the

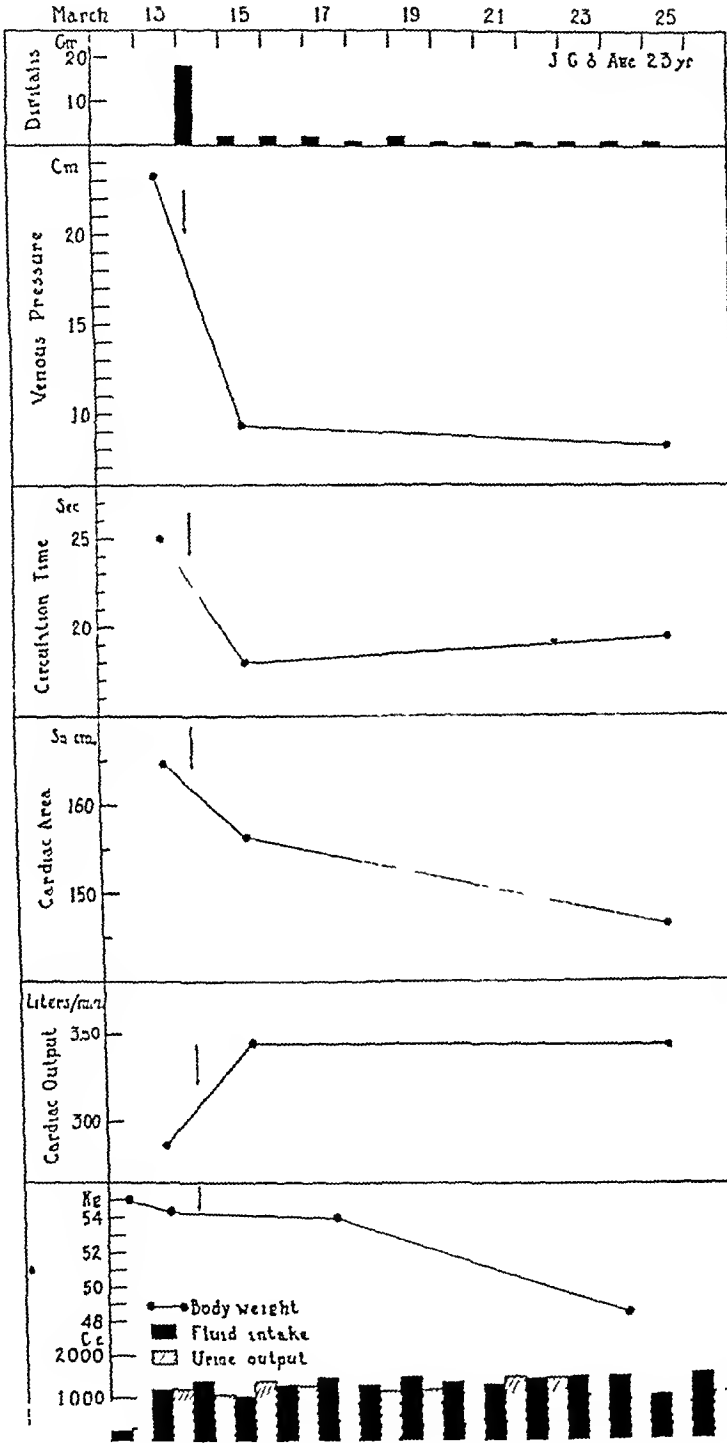


Fig 8—The effect of digitalis on urinary output and body weight, cardiac output, cardiac size, circulation time and venous pressure in case 12 (rheumatic heart disease) In this patient as well as in those whose data are given in figures 10 to 12, auricular fibrillation was present

output per beat was more than doubled (table 2) The signs of heart failure became less Ten days later (March 25), the use of the drug being continued, the cardiac output, circulation time and venous pressure remained unchanged, but the cardiac size was still smaller

TABLE 2—Data Relating to Nine Patients With Con

Case	Age	Sex	Date	Body Surface, Sq M	Oxygen Consumption, Cc per Min	Arterio-venous Oxygen Difference, Cc	Cardiac Output, L per Min	Cardiac Output, L per Sq M per Min	Cardiac Area, Sq Cm	Cardiac Volume, Cc *	Arterial Pressure, Mm Hg	Circulation Time, Sec
12 J G	28	M	3/13/35	1 57	272	95 2	2 86	1 82	164 3	1,920	150 130/ 90	25 4
			3/14/35									
			3/15/35	1 54	267	79 4	3 36	2 18	156 2	1,780	126/ 60	18 0
			3/25/35	1 50	247	74 1	3 33	2 22	146 5	1,615	134/ 65	19 5
13 A C	32	M	3/27/35	1 80	278	119 8	2 32	1 28	171 9	2,057	94/ 56	28 0
			3/28/35									
			3/30/35	1 79	269	84 6	3 20	1 78	163 8	1,910	94/ 52	20 0
			4/ 2/35	1 80	263	78 3	3 36	1 86	154 9	1,737	114/ 76	18 0
14 L O	30	F	3/ 4/35	1 66	222	96 8	2 29	1 38	202 9	2,640	120 110/ 74	22 5
			3/ 5/35									
			3/ 6/35	1 66	207	74 4	2 78	1 70	185 3	2,298	118 110/ 74	20 2
15 M C	53	F	1/23/36	1 61	207	102 9	2 01	1 25	194 2	2,490	170/100	34 0
			1/29/36									
			1/30/36	1 61	201	89 3	2 25	1 40	179 3	2,188	170 162/100	15 8
			2/ 1/36	1 60	197	87 6	2 25	1 40	170 1	2,021	188/105	16 1
			2/14/36	1 60	193	77 8	2 48	1 55	168 7	2,000	150/ 70	22 2
16 G MacF	57	M	2/25/36	1 52	189	84 2	2 24	1 47	153 6	1,821	110/ 90	24 0
			2/26/36									
			2/27/36	1 52	193	84 6	2 28	1 50	153 8	1,740	120/ 74	22 6
			2/29/36	1 51	182	70 8	2 57	1 70	143 1	1,560	118/ 62	19 7
17 J M	37	M	2/27/34	1 72	203	100 5	2 02	1 17	218 0	2,932	140/ 80	
			3/1 3/34									
			3/ 4/34	1 72	221	95 6	2 31	1 34	205 4	2,682	140/ 80††	
18 M P	41	F	4/30/34	1 54	180	90 6	1 98	1 28	173 2	2,079	112/ 70	
			5/ 1/34									
			5/ 2/34	1 54	172	90 6	1 90	1 23	167 3	1,975	105/ 80	
			5/ 5/34	1 52	164	79 9	2 05	1 35	157 2	1,798	105/ 80	
			5/10/34	1 53	159	74 3	2 14	1 40	162 0	1,881	100/ 70	
19 F K	61	M	2/28/35	1 99	240	83 1	2 89	1 45	193 0	2,540	174 160/110	20 1
			3/ 1/35									
			3/ 2/35	1 97	240	74 4	3 23	1 64	169 1	2,005	140 130/ 76	17 9
20 F St J	73	M	9/25/35	1 89	245	94 4	2 60	1 37	166 6	1,960	150/ 90	55 0
			9/26/35									
			9/27/35	1 84	247	77 4	3 19	1 73	156 3	1,779	150 140/ 68	32 8
			10/ 2/35	1 77	241	81 2	3 00	1 70	157 1	1,794	136-130/ 80	33 0

* The volumes have not been multiplied by the constant included in Bardeen's formula, as stated in text

† Apical rate

†† The blood pressure was not taken on these days, the figures obtained on February 27 were used for calculations

The results in the case of A C (case 13) serve to illustrate the course of events in a patient without elevation of the venous pressure (cases 13, 14 and 16) Giving digitalis (18 Gm) resulted in an increase in cardiac output per minute and per beat (table 2 and fig 9), a decrease in cardiac size (fig 10), a shortening of circulation time and no significant change in venous pressure There was relief from the signs and symptoms of congestive heart failure

WORK OF THE HEART

The effect of digitalis on the work of the left ventricle per beat was estimated, as it was for the paper relating to compensated heart disease⁴ Starr and his associates⁵ have found that the work of the left ventricle

gestive Heart Failure Exhibiting Auricular Fibrillation

Venous Pressure, Cm	Vital Capacity, Ce	Cardiac Rate, per Min †	Cardiac Output, Cc per Beat	Work of Left Ventricle, Gm M per Beat	Digitalis, Gm	Diuresis	Diagnosis ‡	Signs of Failure					Fluid in Chest	Red Blood Cell Count and Hemoglobin Values §
								Cyanosis	Liver	Rales	Edema	Dyspnea		
23.2	2,600	102	28	43.8	1.8	+	M.S., M.I., Enl. Ht., IIB	+	+	+	+	+	0	5.7 115
9.3	2,900	52	66	84.7	0.2 q d			0	±	0	0	0	0	
8.1	3,250	60	56	76.2				0	0	0	0	0	0	
7.2	3,500	150	15	15.3	1.8	Lost weight	M.S., M.I., A.I., Enl. Ht., IIB	+	+	+	0	+	0	4.5 95
7.5	4,000	102	32	33.4	0.2 (March 29) q d			0	0	0	0	0	0	
4.7	4,350	72	47	60.7				0	0	0	0	0	0	
6.6	2,750	100	23	31.3	1.7	Slight	M.S., M.I., Enl. Ht., IIB	+	+	0	+	+	0	6.0 107
6.4	2,700	70	40	53.9				0	±	0	0	0	0	
11.4	1,550	100	20	36.7	1.8	0	M.S., M.I., Hpt. Enl. Ht., IIB	+	+	+	+	0	+	5.1 95
6.0	3,000	68	33	37.4	0.2 q d			+	±	0	±	0	±	
5.8	1,900	72	31	62.0				0	0	0	0	0	0	
8.1	2,000	70	35	52.3				0	0	0	0	0	0	
7.9	1,750	84	27	36.7	1.8	+	M.S., M.I., Enl. Ht., IIB	+	+	+	0	0	0	4.6 90
4.6	1,900	78	29	38.3	0.2 q d			0	0	±	0	0	0	
2.9	1,850	68	38	46.5				0	0	±	0	0	0	
	2,700	76	27	40.4	1.0 (3/1) 1.2 (3/2) 0.2 (3/3)	0	M.S., M.I., Enl. Ht., IIB	+	+	+	0	+	0	3.8 92
	2,075	75	31	46.4				↓	↓	0	0	↓	0	
	2,080	124	16	10.8	1.8	0	M.S., M.I., Enl. Ht., IIB	0	+	+	0	0	0	5.1 84
	2,070	86	22	27.8	0.2 q d			0	+	+	0	0	0	
	2,200	71	30	37.9				0	↓	↓	0	0	0	
	2,200	59	36	41.6				0	↓	↓	0	0	0	
17.3	2,200	119	24	44.6	2.0	Lost weight	Aneurysm, Enl. Ht., IIB	+	0	+	+	+	0	5.2 100
12.1	2,750	90	36	52.0				+	0	+	↓	↓	0	
14.8	1,200	60	43	70.2	1.8 ¶	+	Aortic, Enl. Ht., IIB	+	+	+	+	+	0	4.4 86
9.3	1,600	58	55	80.0				↓	↓	↓	↓	↓	0	
8.0	1,800	66	45	65.5				±	±	±	±	↓	0	

† IIA indicates the classification number

¶ This patient received 1.5 Gm. of theocaine three times a day throughout the period of these observations

§ The values for red blood cells are given in millions, those for hemoglobin are given in percentages, 14.5 Gm. of hemoglobin being equivalent to 100 per cent

5 (a) Starr, I., Jr., Collins, L. H., and Wood, F. C. Studies of the Basal Work and Output of the Heart in Clinical Conditions, *J. Clin. Investigation* **12** 13 (Jan.) 1933 (b) Starr, I., Jr., Donald, J. S., Margolies, A., Shaw, R., Collins, L. H., and Gamble, C. J. Studies of the Heart and Circulation in Disease. Estimations of Basal Cardiac Output, Metabolism, Heart Size, and Blood Pressure in Two Hundred and Thirty-Five Subjects, *ibid.* **13** 561 (July) 1934

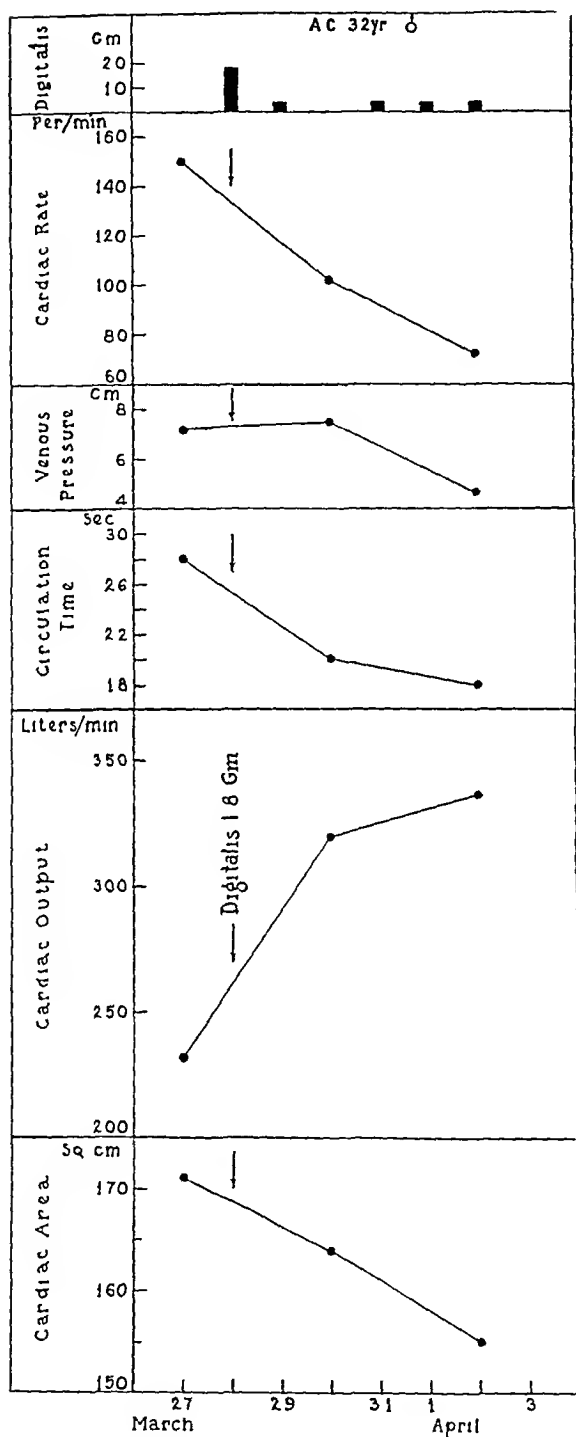


Fig 9—The effect of digitalis on cardiac size, cardiac output, circulation time, venous pressure and ventricular rate in case 13 (rheumatic heart disease) The venous pressure was not elevated during congestive failure in this instance

which is maintaining an adequate circulation bears a linear relation to the size of the heart. From their data they have defined a zone of normal circulatory function. In a manner similar to theirs, we have plotted cardiac volumes as abscissas and gram meters of work of the left ventricle per beat as ordinates (tables 1 and 2 and figs 11 and 12). During failure the values for all the patients except 1 (case 6, normal sinus rhythm) fell below line *CD*, outside the zone of normal circulatory function, whether the rhythm was regular (fig 11) or that of auricular fibrillation (fig 12). When digitalis was given, however, all the values

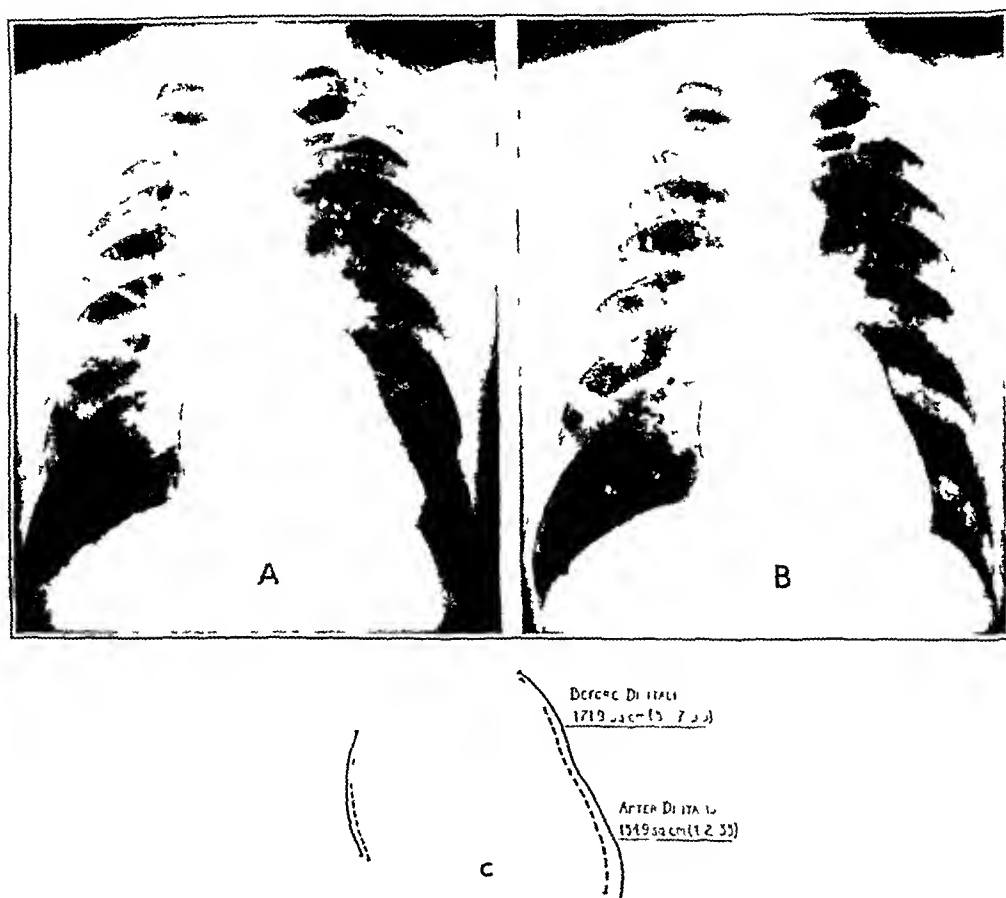


Fig 10—The change in the size of the heart after the administration of 18 Gm of digitalis in case 13. *A* was taken (March 27, 1935) before and *B* (April 2) three days after the administration of the drug. In *C* are shown superimposed the outlines of the heart obtained from tracings of *A* and *B*.

moved closer to or into the zone of normal circulatory function. In short, the work of the left ventricle per beat became more nearly commensurate with what was expected of the heart for its size.

SUMMARY

The cardiac output was decreased, and the heart size was increased in 20 cases of heart failure of the congestive type. The administration of digitalis to 11 of these patients in whom the rhythm was regular and

to 9 with auricular fibrillation resulted in twenty-four hours in an increase in cardiac output, a decrease in cardiac size, a shortening of circulation time, and a fall in venous pressure if it was elevated

Moreover, giving digitalis to these patients increased the work of the heart per beat, a decrease in the size of the heart also having

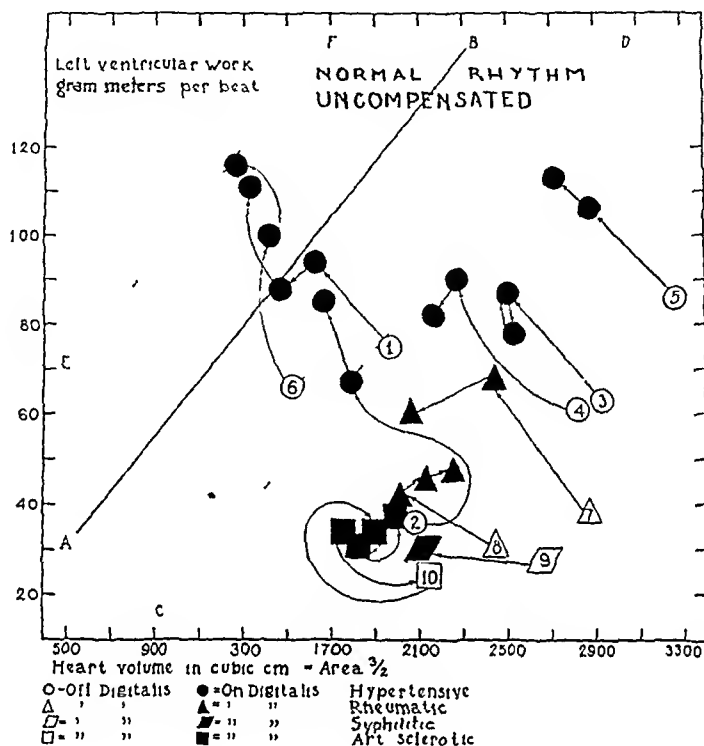


Fig 11—Data relating to the work of the left ventricle per beat and the cardiac volume in cases of congestive heart failure when normal sinus rhythm was present. Data relating to the work of the left ventricle per beat (cases 1 to 10 inclusive, table 1) are plotted against the corresponding cardiac volumes. Line *AB* represents the best line, the regression of the work on the volume, defined by Starr, Collins and Wood^{5a} on the basis of a statistical treatment of data for a control group of cases. Lines *CD* and *EF* were placed by these authors at a distance of twice the standard deviation from *AB*. It appears from their observations that a patient whose values fall within zone *CD-EF* has a normal circulatory function, that is to say, the work of the heart is commensurate with its size, on the other hand, they found that the values relating to patients who had suffered from cardiac decompensation fell in a zone below *CD*. The values for all the patients represented in this figure except L. B. (case 6) fell in the zone below *CD* before digitalis was given, that is to say, in the zone indicative of heart failure. The cause of the heart disease in each case is indicated by the shape of the symbol employed, in accordance with the key shown at the bottom of the figure. Open symbols represent the position of the values before digitalis was given and closed symbols their position after the exhibition of the drug. Arrows indicate the changes in position which occurred after digitalization. It will be observed that in all instances digitalis made the values take up a more advantageous position on the chart, closer to or into the zone of normal circulatory function. This change was particularly marked in cases 1 and 2, the values passing above line *CD*, into the zone of normal circulatory function.

occurred, the work per beat became more nearly commensurate with its size (figs 11 and 12), and the value for the patients moved closer to or into the zone of normal circulatory function

COMMENT

On the basis of our former studies of the action of digitalis⁶ as well as our present observations, we have been able to demonstrate clinically

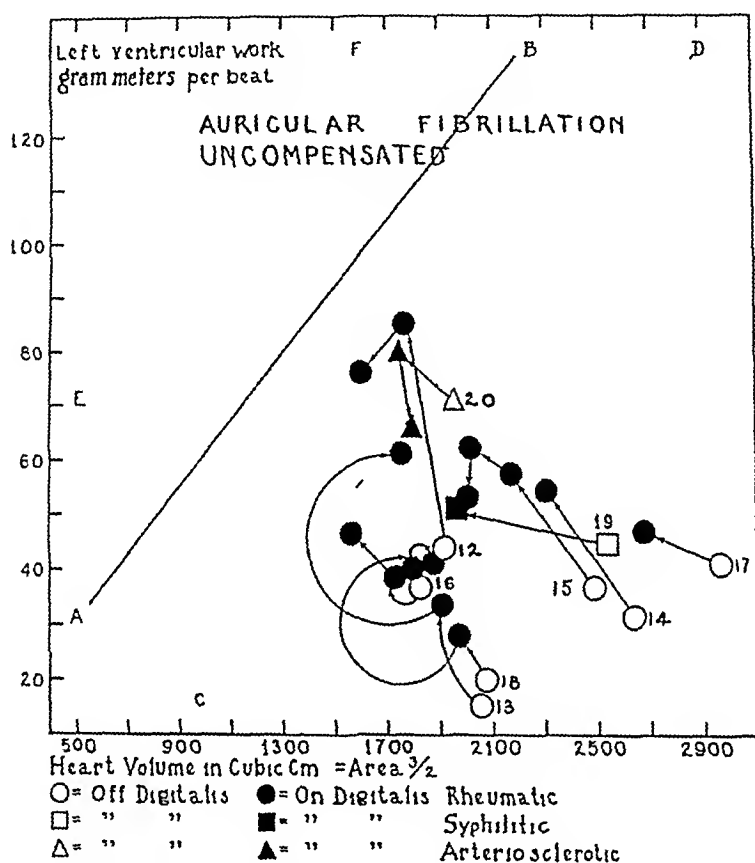


Fig 12—Data relating to the work of the left ventricle per beat and the cardiac volume in cases of congestive heart failure with auricular fibrillation (cases 12 to 20, inclusive, table 2) This chart is made in the same fashion as figure 8 The interpretation of the symbols is identical with that given in figure 8 All the values fell below line CD, outside the zone of normal circulatory function After the exhibition of digitalis, the values in all 9 cases moved closer to CD or even up into zone CD-EF and consequently assumed a more advantageous position on the chart This change was of particular interest in cases 12 and 20, the values passing above line CD, into the zone of normal circulatory function

6 (a) Cohn, A E, and Stewart, H J Evidence That Digitalis Influences Contraction of the Heart in Man, *J Clin Investigation* 1 97 (Oct) 1924, (b) The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs, *ibid* 6:53 (Aug) 1928, (c) The Relation Between Cardiac Size and Cardiac Output per Minute Following The Administration of Digitalis in Dogs in Which the Heart Is Enlarged, *ibid*

certain consequences of giving the drug which may be summarized to present our point of view (table 3) It appears that

1 Digitalis increases the extent of ventricular contraction in man and in dogs ^{6a-c}

2 Digitalis decreases the cardiac output ¹ and the cardiac size ¹ of normal persons without decreasing the venous pressure ¹

3 When digitalis is given to patients suffering from organic heart disease who exhibit regular sinus rhythm without congestive heart failure, it may (a) decrease the size, decrease the output and increase the circulation time, (b) decrease the size, increase the cardiac output and decrease the circulation time or (c) leave the size, cardiac output and circulation time all unchanged The venous pressure was not sig-

TABLE 3—*Actions of Digitalis That May Be Observed Clinically* *

Clinical State	Species	Rhythm†	Changes in T Wave	Heart Rate	Extent of Ventricular Contraction	Cardiac Size	Cardiac Output	Work per Beat	Circulation Time	Venous Pressure
Normal	Dog	N R	Yes	—	+	—	—	?	?	?
	Man	N R	Yes	—	+	—	—	+	?	0
Organic heart disease Without failure	Dog	N R	Yes	—	+	—	—	?	?	?
			Yes	—	+	—	—	+	+	0
			Yes	—	+	0	0	+	0	0
			Yes	—	+	—	+	+	—	0
	Man	A F	Yes	—	+	0	0	+	0	0
			Yes	—	+	—	+	+	—	0
			Yes	—	?	—	+	?	?	?
			Yes	—	+	—	+	+	—	—
	Dog	A F	Yes	—	+	—	+	+	—	—
			Yes	—	+	—	+	+	—	—
With failure	Man	N R	Yes	—	+	—	+	+	—	—
	Dog	N R	Yes	—	+	—	+	?	?	?

* In this table — indicates decrease +, increase, 0, no change ?, not known

† N R indicates normal sinus rhythm, A F, auricular fibrillation

nificantly altered ³ In short, in some cases the heart behaved like a failing heart and in others like a normal one

4 In cases of auricular fibrillation without congestive heart failure, digitalis may increase the cardiac output and decrease the size and circulation time or leave them unchanged, ³ in short, a response may be obtained which is not different from that observed in cases in which the heart is beating regularly

5 In the presence of auricular fibrillation and congestive heart failure, digitalis produces an increase in cardiac output and a decrease in cardiac size and circulation time, and a decrease in venous pressure if it is elevated (earlier ¹ and present observations)

6 79 (Aug) 1928 (d) Stewart, H J, and Cohn, A E Studies of the Effect of the Action of Digitalis on the Output of Blood from the Heart II The Effect on the Output of the Hearts of Dogs Subject to Artificial Auricular Fibrillation, *ibid* 11 897 (Sept) 1932, (e) footnote 1 Stewart, Crane Deitrick and Thompson ³

6 In the presence of normal sinus rhythm in congestive heart failure it appears from the observations now being reported, as well as those already recorded,¹ that digitalis increases the cardiac output and decreases the cardiac size, circulation time and venous pressure

7 In a parallel series of observations on dogs, similar results obtained so far as contraction, cardiac output and cardiac size were concerned^{6b-d}

8 The work of the heart per beat was increased by digitalis in all the cases of heart disease, due to various etiologic factors, which have been studied (earlier³ and present observations), whether failure was present or not and whether there was a regular rhythm or auricular fibrillation

Cattell and Gold⁷ have recently shown that two digitalis glucosides (ouabain and digitoxin) increase the systolic tension in cats, in short, they increase the force of contraction

These data may be fitted together into a concept of the action of digitalis. It is apparent that there are certain uniform actions of the drug, namely, a decrease in size and increase in the extent of contraction, an effect on the electrocardiogram and an increase in the work of the left ventricle. Moreover, these occur irrespective of whether the heart is a normal or a diseased one, whether it is compensated or in failure and whether there is a normal sinus rhythm or auricular fibrillation. The net effect of these actions on the cardiac output, however, differs, depending on whether the heart is dilated or not. That is to say, the action of the drug is the same in all instances, but the consequences of the action on the minute volume of blood from the heart are different, depending on whether the heart is small or dilated. These observations show clearly that an effect on size, namely, a decrease, appears to be an important action of the drug. When the size of the heart changes, the cardiac output alters, when a change in size occurs, it appears to override the effect on contraction^{6b,c}. If the heart is made too small, the cardiac output decreases, but if the heart is dilated and a decrease in size occurs, the drug brings it to a more appropriate size, and an increase in output occurs. Parallel changes in the velocity of blood flow occur. In all instances which we have encountered, digitalis caused an increase in the work performed by the heart per beat and brought the work accomplished more nearly in line with the size of the organ (figures 7 to 9 in our earlier paper³ and figures 11 and 12 in this paper). The explanation of these events may be found in Starling's⁸ theory dealing with the length of the muscle fibers of the heart. In these cases we have

7 Cattell, M., and Gold, H. The Influence of Digitalis Glucosides on the Force of Contraction of the Mammalian Cardiac Muscle, *J. Pharmacol. & Exper. Therap.* 62:116 (Jan.) 1938

8 Starling, E. H. The Lincacre Lectures on the Law of the Heart, Given at Cambridge, 1915, London, Longmans, Green & Co., 1918

demonstrated clear evidence of a change in the size of the heart and an increase in its functional capacity. The correlation of Starr and his associates⁵ points to the same notion, and our observations bear them out.

The observations of Cattell and Gold⁷ which have been mentioned indicate still another action of digitalis on cardiac muscle, namely, an effect on systolic tension. It appears, however, that this is not the most significant action of the drug, for the effect on size appears to override it, just as it overrides the effect of an increase in the extent of ventricular contraction^{6b,c}. There is evidence for this interpretation. In the first place, in normal persons and in certain patients exhibiting heart disease, without congestive heart failure (group 1 in our earlier paper³), digitalis decreased the cardiac output and the cardiac size, even though we have reason to believe that the extent of ventricular contraction increased^{6a} and that the force of contraction increased,⁷ in short, the effect on size in making the pump too small was the predominate one and resulted in a decrease in output, even though an increase in the extent of the contractions and an increase in the force of the contractions were factors influencing the output toward an increase. In the second place, we encountered cases of heart disease without failure (group 3 in our earlier paper³) in which the giving of digitalis brought about no change in cardiac size, in them, however, no change in cardiac output occurred. These results give clear evidence that the effect on size is the most significant one, since when it fails to occur, a change in output also is not apparent.

Friedman, Clark, Resnik and Harrison⁹ have taken issue with our earlier observations relating to heart failure,¹ because in the rebreathing part of the technic two samples of gas were taken instead of three, and relating to the "time" at which our samples were taken. We used the method which was then available. The patients were selected so that the method would be applicable to them, and to this end we chose those whose lungs were relatively free from rales and who, on trial, were found to rebreathe easily, moreover, we took the samples later than was our custom when studying normal persons¹⁰. Furthermore, the amount of gas to be rebreathed was reduced, in proportion to the patient's vital capacity, to the amount which, after training, he could take completely. In addition, duplicate observations were made within fifteen minutes, and checks were obtained. It turns out, now that we have come to

9 Friedman, B., Clark, G., Resnik, H., Jr., and Harrison, T. R. Effects of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure, *Arch Int Med* 56:710 (Oct) 1935.

10 In our earlier paper¹ we stated that samples were taken first after a rebreathing period of fifteen seconds. This statement should have been expanded to include those instances in which the rebreathing time was longer.

repeat these observations on patients as nearly like those whom we previously reported on as possible, making use of the three sample technic, that the results are in agreement with those already published by us. These later results, as did the others, reveal an association between cardiac output and cardiac size, in addition, in the latter observations we have added data relating to the velocity of blood flow. In the light of our newer observations there appears to be no reason to discard our earlier ones.

On the other hand, we have stressed the point that, if any underlying pattern of the actions of digitalis is to be detected, as many factors as possible should be kept uniform. To this end we have selected patients as nearly alike as possible for each group. Since, however, cases that are identical in all respects are not encountered in the clinic, we have stressed uniformity of factors that were in our control, namely, giving to all the patients the same amount of the same "batch" of the drug within the same number of hours and making our observations at comparable times with respect to the giving of digitalis, and, finally, since our observations of normal persons indicated that the effects may occur early, we have continued in the belief that these early effects cannot be ignored. Now that we have shown that our former observations need not be discarded, since the new ones follow the same pattern, we have reexamined Harrison's⁹ data to discover whether apparently different results were not to be reconciled. He said that he could not detect patterns in his results. The apparent difference so far as cardiac output is concerned between our results and Harrison's may be due to differences in the manner in which the observations were carried out. (a) His observations were made at varying times before digitalis was given, while ours were made the day before the drug was given. (b) His observations were made at different times after the drug was given, the first observation being made from one to four days after use of the drug was started, in ours (except on two occasions, see the tables) it was made twenty-four hours after the drug was given. (c) The patients were given different amounts of the drug, and it is not stated whether it was of the same batch and of the same potency, it was not given to all the patients in a uniform fashion. On the other hand, all our patients received the same amount of the drug, from one "batch," on the same schedule. (d) No other drugs were given to our patients which might interfere with recognition or separation of the digitalis effect. (e) There is occasioned some doubt about the value of the method he employed in plotting his charts. The average output before the giving of digitalis was taken as a "zero line." This method may be misleading, since observations were made as far ahead of the giving of digitalis as an average of five days, during this time the cardiac output may have changed as a consequence of a change in the patient's state, if this

occurred, data relating to different states of the patient were averaged and taken as a base line and compared with data secured after the drug was given. Plotting the raw data recorded in his tables, as we have done without this procedure, reveals more accurately the effect of the drug. As a consequence there results a resorting of the patients (tables 1 to 3⁹) to show 12 in whom an increase in output occurred (J E, H M, A E, G B S, C M, P F, L M, L M, M P, A T, F B and S F), 5 in whom no change in output was apparent (I M, M B, T K, M L and Y D) and 5 in whom a decrease in output occurred (M O, L W, G M, A M, and R O) after the giving of digitalis.

It is obvious therefore that the different routines by which his observations and ours were carried out do not make the findings strictly comparable. Nevertheless, when we analyze his data, as already described, by plotting them in the raw, we can detect patterns in his results. He found the cardiac output sometimes increased, sometimes unchanged and sometimes decreased with the giving of digitalis. From his data he said he was unable to establish any correlations with respect to the action of the drug. In certain cases, however, the patients fell into groups similar to those we have described, that is to say, those with an increased cardiac output and those with an unchanged cardiac output. These might have been the ones in whom, in our series, the cardiac size was decreased (group 2³) and unchanged (group 3³), respectively. On the other hand, the patients in whom he found the cardiac output decreased may be similar to the group we have reported on whose cardiac size was made too small and, as a consequence, whose cardiac output was decreased (group 1³). Whether the hearts of his subjects were large or small is not known, and no observations were made relating to the effect of digitalis on the cardiac size. Further speculation on this point is not profitable.

We have not been of the opinion that the action of digitalis can be measured in terms of a single function, such as cardiac output, but it appears that its effects, so far as cardiac output is concerned, can in a measure be correlated with its other effects, namely, the effect on size, on contraction and on work per beat. Furthermore, we have been careful in stating that we do not think that benefit can be gaged in terms of any one effect, such as a change in cardiac output¹. For, although in the patient with compensated heart disease there are divergent effects on the cardiac output per minute, we have shown one phenomenon common to all, with compensated as well as with uncompensated heart disease, namely, that digitalis increases the work of the left ventricle per beat irrespective of its effect on the total output (our earlier³ and our present observations).

We find observations of another sort in the literature which give weight to our interpretation of the results of our studies of the action of

digitalis. These relate to the effect of the drug in the heart-lung preparations and in revived human hearts. With regard to the former, Cohn and Steele¹¹ have reviewed the earlier observations and have contributed data showing that digitalis increases the output of the failing, dilating heart. Peters and Visscher¹² have recently presented data showing that the failing heart suffers a decrease in mechanical efficiency and that digitalis glucosides increase the output and increase the work and "efficiency" of the organ. And, finally, in the case of the revived human heart, Kountz¹³ has shown that the exhibition of digitalis to a patient with such a dilated, failing heart resulted in a marked decrease of the diastolic size and an increase in the flow through the coronary arteries.

CONCLUSIONS

From the detailed study of the mechanism of the action of digitalis on the circulation of 42 patients suffering from heart disease (our earlier³ and our present observations) the following conclusions may be drawn.

The output of blood per minute from the heart which is in failure is diminished, the velocity of the blood flow is less and the heart is larger than when it is in a state of compensation. The work per beat is decreased and is not commensurate with the size of the organ. The venous pressure is in certain instances elevated, and in others it is in the normal range.

Digitalis increases the output per minute of the failing heart, decreases its size and increases the work per beat, so that it more nearly approximates what is expected of it for its size. The circulating blood now moves at a greater velocity. A fall in venous pressure occurs if it was elevated beforehand.

An interpretation of these results in the light of those already reported is that digitalis has the same action on the normal as on the pathologic heart, it decreases the cardiac size, which we interpret as an effect on tone. The amount of the cardiac output which results from this action depends on the initial size of the heart. The amount decreases in the case of a normal heart and increases in the case of a dilated one. Our evidence indicates that digitalis acts in a similar fashion on the normal heart and on those damaged by valvular disease and by myo-

11 Cohn, A. E., and Steele, J. M. Studies of the Effect of the Action of Digitalis on the Output of Blood from the Heart. I. The Effect on the Output of the Dog's Heart in Heart-Lung Preparations, *J. Clin. Investigation* **11** 871 (Sept.) 1932.

12 Peters, H. C., and Visscher, M. B. The Energy Metabolism of the Heart in Failure and the Influence of Drugs upon It, *Am. Heart J.* **11** 273 (March) 1936.

13 Kountz, W. B. The Coronary Flow in Hearts of Individuals Dying of Cardiac Insufficiency, *Am. Heart J.* **12** 490 (Oct.) 1936.

cardial disease unless the myocardial damage is extreme, in which case toxic effects might possibly be elicited at lower concentrations of digitalis

The effect of digitalis in the presence of auricular fibrillation is similar to that recorded when the rhythm is regular

The response of hearts damaged by syphilis, arteriosclerosis and hypertension appears to be similar to that observed for hearts damaged by rheumatic fever

The response of patients whose aortic valves are damaged is not different from that of patients exhibiting mitral involvement

The decrease in cardiac size appears to be the most important effect of digitalis, the change in cardiac output being a consequence of it

The lowering of the venous pressure by the administration of digitalis to the patient exhibiting heart failure seems to be dependent on an increase in cardiac output. An increase in cardiac output and work per beat permits the pumping onward of the blood accumulated on the right side so that a proper distribution results

There are indications that digitalis may benefit certain patients with organic heart disease without heart failure (Christian¹⁴), but the final proof will depend on clinical observations

When considered in the light of our data relating to the action of the drug when the heart is normal¹ and to its action when the heart is damaged by organic heart disease but heart failure is not present, the observations now reported with respect to patients with failure, those presenting regular sinus rhythm as well as those exhibiting auricular fibrillation,³ lead us to restate our original conclusion. Digitalis has similar, perhaps identical, action when the heart is normal and when it is diseased. It decreases the cardiac size and increases the extent of ventricular contraction,^{6a} and to these is to be added the effect on systolic tension (Cattell and Gold⁷). The consequence of these actions is that the cardiac output which results differs, depending on the initial difference in the size of the ventricular cavities in the two situations. In the one (the normal heart and the diseased heart which is not failing) it becomes too small, in the other (the diseased heart which is failing) it acquires a suitable size.

These studies demonstrate, however, a more uniform generalization which is applicable to all these situations, namely, that digitalis increases the work of the heart per beat and that with respect to the heart which is failing, it increases the work per beat and makes it more nearly commensurate with the work expected of the heart for its size.

14 Christian, H. A. The Use of Digitalis Other Than in the Treatment of Cardiac Decompensation, *J. A. M. A.* **100** 789 (March 18) 1933

CLINICAL STUDIES OF RESPIRATION

VII ADDITIONAL OBSERVATIONS CONCERNING THE VALIDITY OF RESULTS OBTAINED WITH THE BODY PLETHYSMOGRAPH

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The use of the plethysmograph in the study of changes in the expiratory volume of the chest has been criticized, and for this reason we wish to report additional observations concerning the validity of this method. Our experiments show that normal persons can be divided into the two following groups. In the first group hyperpnea (voluntary hyperpnea and hyperpnea produced by alteration of the inspired air) is accompanied by a relatively constant oxygen consumption. Spirograms obtained simultaneously with plethysmograms therefore will show the presence or absence of expiratory inflation. In the second group the oxygen consumption is increased during hyperpnea, and the occurrence of expiratory inflation cannot be demonstrated for certain. One may ascertain, however, whether or not expiratory inflation is possible by comparing the volume of the complemental air during rest with the increase produced in the volume of the tidal air during hyperpnea. An increase in the volume of tidal air equal to or greater than that of the complemental air during rest excludes the possibility of expiratory inflation during the observed hyperpnea, whereas if the volume of complemental air during rest exceeds the increase in tidal air by 0.5 to 1 liter or more, expiratory inflation is possible. Proving that expiratory inflation is possible does not signify that it occurs, but we have never observed expiratory deflation beyond that of rest except with coughing or speaking or during forced expiration. Inflation, on the other hand, may occur with any respiratory stimulation.

The results obtained by making simultaneous spiograms and plethysmograms during hyperpnea produced by alteration of the inspired

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air have been published¹ The present report is concerned, first, with a comparison of spiograms with plethysmograms made during voluntary hyperpnea and, second, with a comparison of the increase in volume of tidal air during hyperpnea produced by physical exertion with that of the complemental air during rest

METHOD

For 13 normal men, spiograms and plethysmograms were obtained simultaneously during voluntary hyperpnea

The increase in tidal air following physical exertion was compared with the volume of complemental air during rest in twenty-nine experiments on 9 young men The tidal, complemental and reserve air during rest and the vital capacity were measured by means of a face mask attached to a spirometer, the subject being in the supine position The excursions of the spirometer were recorded and calibrated with a kymograph Each subject first rested for thirty minutes in the supine position with the face mask in place The volume of the tidal air during rest was then obtained without his knowledge by diverting the expired air into the spirometer The volume of complemental air was then estimated at frequent intervals by the usual method The accuracy of these data for the complemental air was confirmed by obtaining the volumes of both the tidal and the complemental air and subtracting the former from the latter The average of fifty or more measurements of tidal air was taken as the volume of tidal air during rest, and the average of ten or more measurements of complemental air was taken as the volume of complemental air during rest The vital capacity was measured in each instance and was found to be proportionate to the volumes obtained for the complemental and the tidal air The volume of tidal air during hyperpnea following physical exertion was measured with the subject in the supine position for one or two minutes immediately after he had performed ordinary stool stepping as rapidly as possible and for as long as he was physically able The volume of the tidal air during rest was subtracted from the volume of the largest respiration, and the resulting volume was compared with the volume of the complemental air during rest According to Peabody and his associates,² the greatest pulmonary ventilation occurs for one or two minutes after exertion

RESULTS

Expiratory inflation occurred in 7 of 13 subjects during voluntary hyperpnea and was demonstrable on both the spiograms and the plethysmograms In the remaining 6 subjects there was no change in expiratory volume by either method

1 Greene, J A Clinical Studies of Respiration III Influence on the Expiratory Position of the Chest in Man of an Inspired Air Which Is Low in Oxygen and High in Carbon Dioxide, and of Resistance to Inspiration and to Expiration, *Arch Int Med* 52 447-453 (Sept) 1933

2 Peabody, F W, Sturgis, C C, Barker, B I, and Read, M N Clinical Studies on the Respiration IX The Effect of Exercise on the Metabolism, Heart Rate, and Pulmonary Ventilation of Normal Subjects and Patients with Heart Disease, *Arch Int Med* 29 277-305 (March) 1922

It is to be noted from the accompanying table that in all instances the volume of the complemental air during rest exceeded the increase produced in the volume of the tidal air

COMMENT

The results obtained with simultaneous spiograms and plethysmograms of voluntary hyperpnea corroborate the results reported previously during hyperpnea produced by alteration of the inspired air ¹

*Summary of Data **

Subject	Volume of Complemental Air During Rest, Cc	Increase in Volume of Tidal Air, Cc	Difference, Cc
R H	2,216	1,204	1,012
		1,457	759
		1,238	978
		1,996	220
		1,595	621
J G	2,443	1,741	702
		1,733	710
		2,073	370
		1,711	732
		1,581	862
H B	3,187	1,619	824
		1,379	1,608
		1,428	1,759
		2,076	1,111
		2,040	1,147
K	2,195	1,547	1,640
		2,371	816
		1,309	1,878
		1,684	511
		1,609	586
C	3,055	1,637	558
		1,783	1,302
R	2,989	1,765	1,224
		2,283	706
G	2,630	1,346	1,284
		1,970	1,160
E	2,962	2,209	753
		1,723	1,239
P	2,632	1,607	1,025

* The volume of complemental air during rest exceeded the increase produced in the tidal air by hyperpnea following physical exertion

The fact that the volume of tidal air during hyperpnea produced by severe muscular exertion does not increase sufficiently to equal the volume of complemental air during rest does not signify that expiratory inflation occurs, but it does show that the expiratory volume of the chest can increase even when the most extreme demands are being made on the respiratory mechanism. In only 2 instances (R H and J G, as shown in the accompanying table) was the difference in the two volumes so slight that expiratory inflation undoubtedly could not have occurred. In both of these experiments the physical exertion was so strenuous that

circulatory collapse appeared imminent. Such a tremendous demand on the respiratory mechanism rarely occurs and was not produced in any of our previous studies.

SUMMARY

Additional observations regarding the validity of results obtained by means of the body plethysmograph are reported. The changes in the expiratory volume of the chest recorded on plethysmograms during voluntary hyperpnea were confirmed by spiograms made simultaneously.

A comparison of the volume of the complemental air during rest with the increase in volume of the tidal air during hyperpnea produced by strenuous muscular exertion shows that expiratory inflation is possible during hyperpnea thus produced.

PNEUMONIA COMPLICATED BY ACUTE PNEUMOCOCCIC HEMORRHAGIC ULCERATIVE GASTRO-ENTERITIS (DIEULAFOY'S EROSION)

REPORT OF TWO CASES

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AND

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The universal omission from standard American textbooks of mention of gastrointestinal ulcerations complicating pneumonia has prompted us to report 2 cases in which treatment was given to patients in the wards of the John Gaston Hospital. It has occurred to us that this complication may not be as rare as the sparsity of reported cases indicates. Search of the literature available to us reveals reports of only 9 cases, the great majority of these from the French literature.

This complication of pneumonia was first described by Dieulafoy,¹ in 1899. He described 2 cases, the first occurring in a patient with lobar pneumonia in whom severe abdominal pain, hematemesis and melena developed. Autopsy revealed multiple acute ulcerations of the stomach, ranging from the size of a pinpoint to a diameter of 3 mm, most of them being grouped in the pyloric region. By a strange coincidence Dieulafoy had in one of his wards at the same time a patient with lobar pneumonia with abdominal symptoms of unusual severity. On the eighth day of the disease this patient vomited a quart (1 liter) of blood but did not die until the nineteenth day of illness, after pneumococcic meningitis had developed. Examination of the stomach revealed

congestion of the mucous membrane but no active erosions, as in the previous case. The histologic examination of the mucosa showed small hemorrhagic foci, some in the submucous tissue and others, more numerous, in the interglandular tissue. These foci (the origin of the hematemesis) pushed the glands aside and formed distinct masses that were separated from the exterior by a thin layer of mucous membrane. Around the foci no trace of inflammatory reaction was to be seen. The search for micro-organisms was fruitless.

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1 Dieulafoy, G. *Gasterite ulcereuse pneumococcique*. Grandes hematemeses, in *clinique medicale de l'Hôtel Dieu de Paris*, Paris, Masson & Cie, 1899, lesson 11, p. 219.

Dieulafoy proposed for this condition the name pneumococcic hemorrhagic ulcerative gastritis

Chatard,² in 1926, collected from the literature reports of 8 cases of gastrointestinal hemorrhage associated with pneumococcic infection. The ages of these patients ranged from 17 to 51 years. Although it was at times difficult to estimate the exact date of onset of the pneumococcic infection, Chatard observed that in the great majority of cases the hemorrhages occurred between the fifth and the twelfth day of the disease, but in Vialard's patient the bleeding took place on the twenty-seventh day of illness.

Chatard classified the gastrointestinal complications of pneumonia as follows:

- 1 Simple enteric
- 2 Dysenteric
- 3 Ulcerating hemorrhagic
 - (a) Ulcerating
 - (b) Hemorrhagic

His simple enteric type of complication consisted of tympanites with its accompanying respiratory embarrassment. It is the most common of all complications and is probably the result of profound toxemia rather than of actual invasion of the abdominal viscera by the pneumococci, since it is prevalent in cases of lobar pneumonia in which repeated cultures of the blood are sterile.

The dysenteric type, as the name implies, is a complication in which the symptoms consist of tenesmus, blood-streaked stools and the other well known manifestations of acute dysentery. It is more severe and exhausting than the simple enteric type.

Chatard divided the third type, the ulcerating hemorrhagic type, into two types. The first of these is the ulcerating type, in which there is formation of one or more ulcers of the stomach or intestine without immediate symptoms. The recognition of this variety rests on careful examination of the stools for occult blood, as there is no frank hemorrhage, at least there was none in the case he reported. The case reported by Claus probably was of this type. His patient was ten days convalescent from a pneumococcic infection when ulcers of the lesser curvature of the stomach and of the descending colon ruptured, resulting in generalized peritonitis.

However, 8 of the 9 reported cases and both of our cases were of the frankly hemorrhagic type. An analysis of this group of cases reveals that the predominating initial symptom was abdominal pain of unusual

2 Chatard, J. A Case of Intestinal Hemorrhage in Pneumococcal Infection, with Clinical Remarks, *M. J. & Rec.* **123** 453 (April 7) 1926.

severity, which was located in the epigastrium, was more or less constant and was nonradiating. However, in Chataid's case there were pains not only in the epigastrium but also in the lumbar regions. These lumbar pains were probably due to acute hemorrhagic nephritis, which he stated was present as a result of profound toxemia. In this case the pain was intermittent, lasting for periods of thirty minutes, which was in contrast to the continuous type of pain usually observed. Along with abdominal pain, nausea and vomiting were usually present in these cases, but in only about one-third did hematemesis occur. In the remainder there was melena, or enterorrhagia. In 1 of Dieulafoy's cases and in 1 of our own cases both hematemesis and melena occurred.

Besides the abdominal symptoms, these patients usually had all the manifestations of internal hemorrhage, namely, a fall in temperature and blood pressure, restlessness and an increasingly weak, rapid, irregular, thready pulse.

Johnson,³ in 1929, reported the case of a boy aged 12 years who had a hemorrhage of 1 pint (500 cc) from the bowel complicating lobar pneumonia which seemed to have been preceded by influenza. An unusual point in his case was that in spite of the hemorrhage the temperature remained at 104 F for some time.

REPORT OF CASES

CASE 1—A H, a white man aged 53 years, was admitted to the John Gaston Hospital on Feb 2, 1936, complaining of pain in the left side of the chest, cough, fever and general malaise. The onset of illness was eleven days prior to entry, when the patient contracted a cold accompanied by a cough which became progressively worse. Five days before admission to the hospital he had three distinct chills about eight hours apart, each followed by high fever, aching of the bones and delirium. The night before entry he was awakened by a stabbing pain in the left side of the chest which was made worse by respiration and cough.

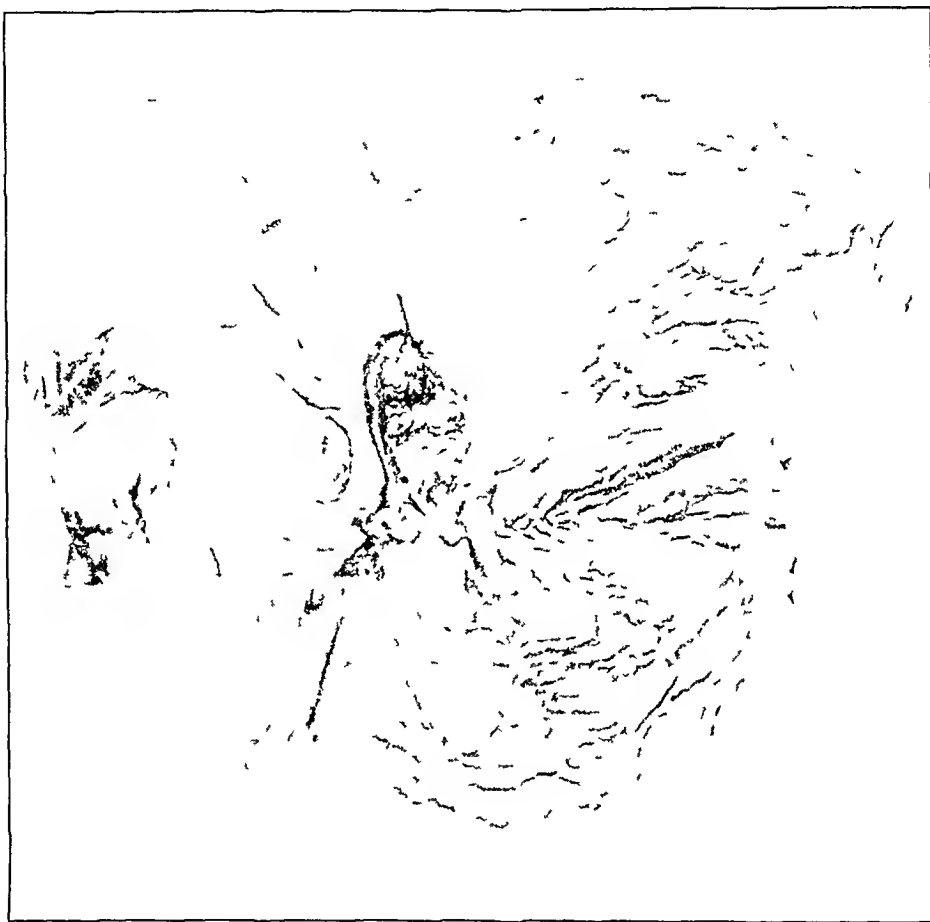
The past and family histories contained nothing of importance relative to the present illness.

Physical examination disclosed all the signs of consolidation of the lower lobe of the left lung. These findings were confirmed by roentgenologic examination, which revealed also areas of increased density characteristic of lobular pneumonia in the upper lobe of the left lung and the lower lobe of the right lung. All the peripheral arteries were moderately resistant to compression. Examination otherwise revealed an essentially normal condition.

The urine contained an occasional granular cast. The red blood cell count and hemoglobin value were slightly below normal, the leukocyte count was 19,000. Later the leukocyte count reached 40,000 and then dropped to 11,000. The percentage of granulocytes remained approximately 89 throughout the disease. The sputum revealed type IV pneumococci. Culture of the blood also showed type IV pneumococci.

3 Johnson, W M. Intestinal Hemorrhage as a Complication of Pneumonia, *Arch Pediat* 44 193 (March) 1929.

The patient's temperature was irregular, ranging from below normal to 105 F. On the eighth day of the disease, signs of empyema on the left side appeared. During the last three days in the hospital the temperature was sub-normal continuously, while the pulse and respiratory rates mounted. The blood pressure decreased, ranging between 115 systolic and 50 diastolic and 70 systolic and 30 diastolic. The general trend of the disease showed a progressive increase in severity, with a diminution of the patient's resistance. On the afternoon of February 11, nine days after admission to the hospital, the patient vomited about 2 ounces (60 cc) of dark red blood and the following day passed a large amount



Photograph of the stomach of our first patient, showing one large ulcer and several smaller ones

of blood in the stool. He died on the morning of February 13. The clinical diagnosis was (1) bronchopneumonia, type IV pneumococci, (2) pneumococcal bacteremia, type IV pneumococci, (3) acute pneumococcal hemorrhagic ulcerative gastritis, (4) empyema on the left side, and (5) generalized arteriosclerosis.

Necropsy Observations—The salient points were scarring of the upper lobe of the left lung, confluent bronchopneumonia of the lower lobe of the left lung, bronchopneumonia of the lower lobe of the right lung, seropurulent empyema on the left and parenchymatous degeneration of the viscera. The stomach and intestines contained large amounts of clotted blood. In the fundus of the stomach (as shown in the accompanying figure) near the center of the lesser curvature

was a large ulceration, 4 cm in diameter, extending down to the muscular coat, in the base of which was an eroded blood vessel. Adjacent to this ulcer were six smaller and more superficial ulcerations. Sections through the largest ulcer were seen microscopically to contain serum, fibrin, leukocytes, dead cells and bacteria. The margin of the ulcer showed necrosis down to the serosa, with a greatly thickened submucosa.

CASE 2—P. P., a Negro aged 26 years, was admitted to the John Gaston Hospital on March 17, 1936. His illness began four days prior to entry, with sore throat, general malaise and fever. Soon a cutting pain developed under the left breast which was aggravated by cough and deep inspiration, and he began to raise brownish sputum.

Examination revealed evidences of pneumonia of the lower lobe of the left lung. Those findings were confirmed by roentgenologic examination. The urine contained a few hyaline and granular casts. Slight anemia was present. The leukocyte count was 10,800, with 93 per cent polymorphonuclear cells. Typing of the sputum disclosed type IV pneumococci. Repeated cultures of the blood were sterile. No other abnormal findings were detected.

Two days after admission to the hospital the patient became delirious and remained so until about six days before discharge. At that time also, definite evidences of consolidation of the lower lobe of the right lung appeared. On March 23, the eleventh day of the disease, the patient began to complain of pain in the epigastrium, and examination revealed tenderness and slight muscular rigidity between the umbilicus and the xiphoid. His temperature dropped from 103 to 99 F, and, strange to say, his pulse rate dropped with it. A tentative diagnosis of acute gastrointestinal ulceration was made, and a few hours later the patient passed by rectum about 5 ounces (150 cc) of blood, the first portion was tarry black and the last dull red. In two days the epigastric tenderness and pain had disappeared, and there was no repetition of the bleeding. He was discharged on April 4, the twenty-third day of the disease, in good condition. The clinical diagnosis was (1) lobar pneumonia (the lower lobes of both lungs) due to type IV pneumococci and (2) acute pneumococcic hemorrhagic ulcerative gastritis or enteritis.

COMMENT

A point of striking coincidence in our 2 cases is that the infecting organisms in both cases were type IV pneumococci. In the first case these organisms were found in the blood stream as well as in the sputum. In the second case the blood was cultured only once prior to the hemorrhage. After the complication, four cultures were sterile. It is most unfortunate that we did not culture the blood daily in this case. In none of the 9 cases reported in the literature was the type of pneumococcus mentioned. Was it mere chance that both our patients were infected with type IV pneumococci, or will future reports by other observers show that this type is particularly likely to cause gastrointestinal ulceration?

In neither of our cases were we able to elicit a history of indigestion, abdominal pain related to meals or any other symptoms suggestive of peptic ulcer antedating the pneumococcic infection. In the first case we

were able to see at necropsy that all the ulcerations were recent. In the second case, in the absence of a history suggestive of peptic ulcer and in the presence of abdominal pain, tenderness and muscular rigidity and of melena, we believe we were justified in making a diagnosis of acute pneumococcic hemorrhagic ulcerative gastritis or enteritis.

It is interesting to note that gastric ulcers occurring in the course of pneumococcic infections have been studied experimentally in the guinea pig. Dieulafoy⁴ cited the experiment by Bezançon and Griffon in which the peritoneum of a healthy guinea pig was inoculated with virulent pneumococci. The animal succumbed in twenty-one hours, and postmortem examination revealed petechiae in the mesentery and large intestine and hemorrhagic nodules in the spleen. The mucosa of the stomach was studded with about fifteen hemorrhagic erosions. Histologic examination of these erosions showed that the process affected only the mucous and submucous coats and that pneumococci were present in the ulcers, as they were in all the organs. This experiment is particularly interesting from two standpoints. First, it revealed the organisms in the ulcerated tissue. Second, it possibly demonstrated another route by which the pneumococcus may attack the gastric mucosa, namely, by way of the peritoneum. Dieulafoy called attention to Griffon's case, in which acute ulcerations were present in the stomach of a woman who died of pneumonia but no pneumococci could be found in the ulcers. The question was therefore raised as to whether ulceration is invariably due to invasion by pneumococci or to its toxins without invasion. Both of Dieulafoy's patients had complicating pneumococcic peritonitis, but in our patient who came to necropsy there was no evidence of peritoneal infection. The following questions we are not able to answer: Is the presence of the pneumococcus in the wall of the gastrointestinal tract necessary for the production of ulceration, or may it be produced in some instances by pneumococcic toxins? If the presence of organisms is essential to the production of ulceration, must they reach the tissue only through the blood stream, or may they also invade the mucosa from the gastrointestinal canal or by extension from the peritoneum?

In view of our experiences with these 2 cases we consider it important to understand the significance of melena or hematemesis complicating pneumonia. Unfortunately Chatard did not append a bibliography to his article, nor did he note the mortality rate in his own series, but since both of Dieulafoy's patients, Griffon's patient and 1 of our patients died, it is inferred that this complication constitutes a serious prognostic omen.

As to therapy, we have nothing new to offer. Both of our patients received conservative medical treatment for gastrointestinal hemorrhage.

⁴ Dieulafoy, G. *A Text-Book of Medicine*, ed 15, New York, D. Appleton and Company, 1911, p. 658.

CONCLUSIONS

We have been able to find in the literature reports of only 9 cases of acute pneumococcic hemorrhagic ulcerative gastroenteritis complicating pneumonia. To these we add reports of 2 new cases.

Hematemesis, melena, abdominal pain, tenderness and muscular rigidity, and a fall in blood pressure and temperature with an increase in pulse rate, in the presence of pneumonia, should lead one to suspect this complication.

This important complication of pneumonia is not discussed in any of the standard American textbooks of medicine.

It is probable that the condition is more frequent than is indicated in the literature.

DIABETES INSIPIDUS AS A SIGN OF METASTATIC INVOLVEMENT OF THE SUPRAOPTICO-HYPOPHYSIAL SYSTEM

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Diabetes insipidus as a clinical manifestation has long been a subject of interest and controversy. The latter has resulted in an accumulation of clinical and experimental data which has tended to clarify the concept of the mechanism of diabetes insipidus. A complete review of the literature of the subject of diabetes insipidus would literally inundate the reader with watery references. However, for want of space, reference to several notable surveys, presented from different points of view, will indicate the extent of the literature and serve as source material.

Staemmler,¹ in 1932, in an extensive review of the subject up to that time, presented evidence indicating that isolated lesions involving the posterior and intermediate lobes of the pituitary body or the hypothalamus may lead to diabetes insipidus. Roussy and Mosinger² and Leschke,³ in 1933, in separate reviews showed the evidence favoring the hypothalamic origin of diabetes insipidus. More recently the outstanding experimental investigations of Ranson and his group of workers⁴ have drawn together the loose ends and have tended to present

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1 Staemmler, M. Diabetes insipidus und Hypophyse, *Ergebn d allg Path u path Anat* **26** 59, 1932.

2 Roussy, G., and Mosinger, M. Le tuber cinereum et son rôle dans les principales fonctions du métabolisme, métabolisme de l'eau, des glucides et des lipides, *Ann de méd* **33** 193, 1933.

3 Leschke, E. Diabète insipide et système hypothalamo-hypophysaire, *Ann de méd* **33** 261, 1933.

4 (a) Fisher, C., Ingram, W. R., and Ranson, S. W. The Relation of the Hypothalamico-Hypophyseal System to Diabetes Insipidus, *Arch Neurol & Psychiat* **34** 124 (July) 1935. (b) Fisher, C., Ingram, W. R., Hare, W. K., and

(Footnote continued on next page)

a harmonious concept of the pathogenesis of diabetes insipidus They have said

The evidence from this investigation supports the theory that diabetes insipidus is a hormonal disturbance, caused by a deficiency in the secretion of the anti-diuretic principle by the pituitary gland The view is set forth that the supra-optico-hypophyseal system sends secretory impulses to these divisions of the hypophysis and that damage to this system at one of three points, the nucleus, the fiber tract and the pars intermedia and pars neuralis, results in diabetes insipidus

Findley⁵ (1937) has traced the origin of the conflicting theories concerning diabetes insipidus and has shown the relation of this disorder to the function of the thyroid gland

Diabetes insipidus, representing a disturbance in the normal functioning of the supraopticohypophysial system, may be due to many conditions which implicate that system Fink⁶ (1928), reviewing the necropsy records of 107 patients with diabetes insipidus, cited the following etiologic factors functional nervous disturbances, such as hysteria, migraine, epilepsy and severe fright, pregnancy, injuries to the base of the skull, syphilitic basal meningitis, tuberculous meningitis, convalescence from acute infectious diseases, epidemic encephalitis, tumors of the midbrain, the hypophysis and the region of the third ventricle, metastatic lesions involving the posterior lobe of the pituitary body and gliomas of the optic chiasm Of the 107 patients, 63 per cent had a tumor at the base of the brain or in the posterior cranial fossa which involved more than one structure at the base of the brain and hence was not of localizing value as regards the appearance of diabetes insipidus

Ranson S W The Degeneration of the Supraoptico-Hypophyseal System in Diabetes Insipidus, *Anat Rec* **63** 29, 1935 (c) Ingram, W R, and Barris, R W Diuresis Associated with Direct Stimulation of the Hypophysis, *Endocrinology* **19** 432, 1935 (d) Ingram, W R, Fisher, C, and Ranson, S W Experimental Diabetes Insipidus in the Monkey, *Arch Int Med* **57** 1067 (June) 1936 (e) Fisher, C, and Ingram, W R The Effect of the Feeding of Thyroid Extract or Salt and of Thyroidectomy on the Fluid Exchange of Cats with Diabetes Insipidus, *ibid* **58** 117 (July) 1936 (f) Ingram, W R, and Fisher, C The Relation of the Posterior Pituitary to Water Exchange in the Cat, *Anat Rec* **66** 271, 1936 (g) Fisher, C, and Ingram, W R The Effect of Interruption of the Supraoptico-Hypophyseal Tracts on the Antidiuretic, Pressor and Oxytotoxic Activity of the Posterior Lobe of the Hypophysis, *Endocrinology* **20** 762, 1936 (h) Fisher, C The Site of Formation of the Posterior Lobe Hormones, *ibid* **21** 19, 1937 (i) Ingram, W R, and Fisher, C The Effects of Thyroidectomy, Castration, Anterior Lobe Administration and Pregnancy upon Experimental Diabetes in the Cat, *ibid* **21** 273, 1937

5 Findley, T Thyroid-Pituitary Relationship in Diabetes Insipidus, *Ann Int Med* **11** 701, 1937

6 Fink, E B Diabetes Insipidus A Clinical Review and Analysis of Necropsy Reports, *Arch Path* **6** 102 (July) 1928

In 14 per cent of the cases reviewed by Fink there was a discrete metastatic carcinomatous nodule limited to the posterior lobe of the hypophysis or to the infundibulum. He stated, "When polyuria develops in a case of malignancy, it is almost a pathognomonic sign of a metastasis in the posterior lobe of the hypophysis." In view of the evidence that involvement of any portion of the supraopticohypophysial system may produce diabetes insipidus, it is well to consider the occurrence of polyuria in a patient with a malignant growth as an indication of metastatic invasion of the whole or of a part of that system.

Since the publication of the review of case reports collected from the literature by Fink,⁶ other cases have been reported in which diabetes insipidus occurred in patients with metastatic lesions involving the hypothalamicohypophysial system. Futcher⁷ reported a case of diabetes insipidus due to metastatic involvement of the hypothalamus (the pituitary body remaining entirely free from metastasis) secondary to primary carcinoma of the lung. Elmer, Kedzierski and Scheps⁸ reported a case of hypernephroma with metastasis to the hypothalamus producing diabetes insipidus. Grassmann⁹ described a case of diabetes insipidus following carcinoma of the breast in which metastatic lesions occurred in the posterior lobe of the pituitary body, and in the tuber cinereum, with little involvement of the anterior lobe and none of the diencephalon. Arnstein,¹⁰ who has stated the belief that the posterior lobe of the pituitary body is intimately associated with control of water metabolism, reported 4 cases of diabetes insipidus resulting from metastatic carcinosis of the posterior lobe of the pituitary body. In two of the cases the condition was secondary to carcinoma of the breast, and in 2 other cases it was secondary to bronchogenic carcinoma. Multiple metastases to the brain developed in 2 cases. The posterior lobe was involved in all the cases, the stalk in 2 cases, the anterior lobe in 2 cases and the capsule in 1 case. In a report of 3 cases of diabetes insipidus Biggart¹¹ described 1 case that was due to multiple carcinomatous metastases to the brain, involving the whole of the posterior lobe of the pituitary

7 Futcher, T. B. Diabetes Insipidus and Lesions of the Mid-Brain. Report of a Case Due to a Metastatic Tumor of the Hypothalamus, *Am J M Sc* **178** 837, 1929.

8 Elmer, A. W.; Kedzierski, J., and Scheps, M. Ein Fall von Diabetes insipidus verursacht durch eine Metastase eines Hypernephroms im Zwischenhirn. Beitrag zur Pathogenese des Diabetes insipidus, *Wien klin Wchnschr* **41** 591, 1928.

9 Grassmann, W. Diabetes insipidus bei Tumormetastasen in der Hypophyse, *Frankfurt Ztschr f Path* **42** 384, 1931.

10 Arnstein, A. Diabetes insipidus bei metastatischer Karzinose der Hypophyse, namentlich des Hinterlappens bei primarem Bronchus- und Mammakarzinom, *Med Klin* **29** 1679, 1933.

11 Biggart, J. H. Diabetes Insipidus, *Brain* **58** 86, 1935.

body, the infundibulum, the hypothalamus and a small part of the anterior lobe of the pituitary body. The primary growth was presumably in the alimentary tract. Macchioro¹² reported a case of metastatic bronchogenic carcinoma involving the hypophyseal system and producing diabetes insipidus. In the case of diabetes insipidus reported by Urechia¹³ the primary lesion was an alveolar carcinoma of the stomach, with metastasis to the entire posterior lobe of the pituitary body, a large part of the intermediate lobe and parts of the anterior lobe and tuberal region.

In the light of so much excellent material on this topic, we lay claim to justification for presenting the following case report because of the unusual features of both hematogenous and lymphogenous metastases of a bronchogenic carcinoma, the former producing diabetes insipidus by involvement of the posterior lobe of the pituitary body and of the infundibulum and the latter resulting in involvement of the serous membranes of the abdominal and thoracic organs with tubercles.

REPORT OF A CASE

History—W. S., a man aged 64 years, a baker, entered the Jewish Hospital on Dec 3, 1936, complaining of polydipsia, polyuria and anorexia of four months' duration. His past medical history was unimportant. He noticed the symptoms in August and several weeks later observed that he was growing weak. He ate little solid food but drank 3 or 4 quarts (3 or 4 liters) of milk daily, in addition to several glasses of water. However, there was no loss of weight, the patient maintaining his usual average of 160 pounds (72.6 Kg). There was no pain, vomiting, hematemesis or melena.

General Examination—On admission to the hospital the patient was fairly well nourished. The routine physical examination revealed no abnormality except a coated tongue, a foul breath and an area of bronchovesicular breathing on the left side of the chest at the seventh interspace posteriorly. The blood pressure was 120 systolic and 70 diastolic. The temperature varied from 97 to 100 F.

Course—The patient remained in the hospital thirty-five days without showing any definite improvement. The daily urinary output varied from 1,000 to 4,890 cc. One cubic centimeter of solution of posterior pituitary U. S. P. given hypodermically on December 10 and 1 cc of solution of posterior pituitary double U. S. P. strength on December 12 caused a marked diminution in the excretion of urine. However, after each injection the patient became apprehensive and agitated. The pulse rate increased and the face became flushed. He subsequently refused all further medication of this nature.

On Jan 7, 1937, the patient left the hospital unimproved, his weight at that time being 155 pounds (70 Kg).

The following day, January 8, the patient became unconscious while walking along the street and was brought immediately to the hospital. Examination dis-

12 Macchioro, G. Su un caso di diabete insipido da tumore metastatico della regione ipofisaria, *Minerva med* **1** 668, 1935.

13 Urechia, C. I. Cancer métastatique de la région hypophyso-tubérienne avec diabète insipide, *Paris méd* **2** 129, 1936.

closed rotatory nystagmus and left hemiplegia. The blood pressure was 150 systolic and 60 diastolic. Pulmonary edema supervened, and death occurred at 4 05 a m the following morning.

Laboratory Data—Many examinations of the urine showed that the specific gravity varied from 1 002 to 1 010, there was a trace of albumin but no sugar. On microscopic examination a few white blood cells were observed occasionally. The volume of urine varied from day to day, the minimum (1,000 cc) being voided on December 23 and the maximum (4,890 cc) on December 7.

Eight blood counts from Dec 4, 1936, to Jan 6, 1937, showed that the hemoglobin value varied from 85 to 104 per cent, the erythrocyte count varied from 4,500,000 to 5,350,000 per cubic millimeter, the leukocyte count averaged 8,700 per cubic millimeter and the average differential count showed 74 per cent polymorphonuclear cells, 24 per cent lymphocytes and 2 per cent eosinophils.

Chemical analysis of the blood on December 4 showed a sugar content of 81 mg per hundred cubic centimeters and a urea nitrogen content of 16 mg. A sugar tolerance test gave the following values: 81 mg during fasting, 111 mg at one-half hour, 206 mg at one hour and 111 mg at two hours. All specimens of urine during this test were free from sugar.

A phenolsulfonphthalein test, made on December 16, indicated a 55 per cent output for the first hour and a 10 per cent output for the second hour. The Fishberg test gave the following results: first specimen, 166 cc, with a specific gravity of 1 010, second specimen, 57 cc, with a specific gravity of 1 013, and, third specimen, 50 cc, with a specific gravity of 1 010. A urea clearance test showed a 70 per cent normal function with the first specimen and a 64 per cent normal function with the second.

Wassermann tests of the blood and spinal fluid gave a negative reaction. The colloidal gold curve was 0000000000.

Fractional gastric analysis showed the following:

		Minutes							
	Residuum	15	30	45	60	75	90	105	120
Free hydrochloric acid	10	25	30	35	50	70	70	80	80
Total acidity	25	35	65	70	70	90	100	110	105

The microscopic study of the various gastric specimens revealed essentially no abnormality.

Roentgen studies, including the skull, chest, gastrointestinal tract and gall-bladder, were reported as follows:

On December 7 the sella turcica presented a normal appearance. There was no evidence of erosion or destruction of the floor, clinoid processes or dorsum sellae. No encroachment was noted in the phenoid sinus. It measured 5 by 10 mm, which was within normal limits. There was slight calcification in the pineal gland, which was not displaced in the lateral view. There was some condensation of bone in the frontal area, which was of no etiologic importance as to the presence of any intracranial lesion.

The heart, right lung and diaphragm were normal. A dense area in the upper field of the left lung was limited to the interlobar fissure and presented the appearance of an inflammatory consolidation, presumably subacute interlobar pleurisy associated with the pneumonitis in the adjacent fields.

The cholecystogram was negative, as was the roentgenogram of the gastrointestinal tract except for signs of an irritable colon.

On January 4 the calcium content of the blood was 112 mg, and the phosphorus content was 4 mg per hundred cubic centimeters. On January 8 the

sugar content was 107 mg, the urea nitrogen content was 20 mg and the carbon dioxide-combining power was 55 volumes per cent

Gross Postmortem Observations—The body was that of an obese aged man. There was no edema of the lower extremities.

There was no excess fluid in the serous cavities. A normal amount of light amber pericardial fluid was present. The parietal pericardium, especially the portion covering the left ventricle, showed a number of firm, elevated, grayish white nodules, 1 or 2 mm in diameter. There were no nodules on the visceral pericardium except in one area near the base of the heart in the region of the interventricular septum.

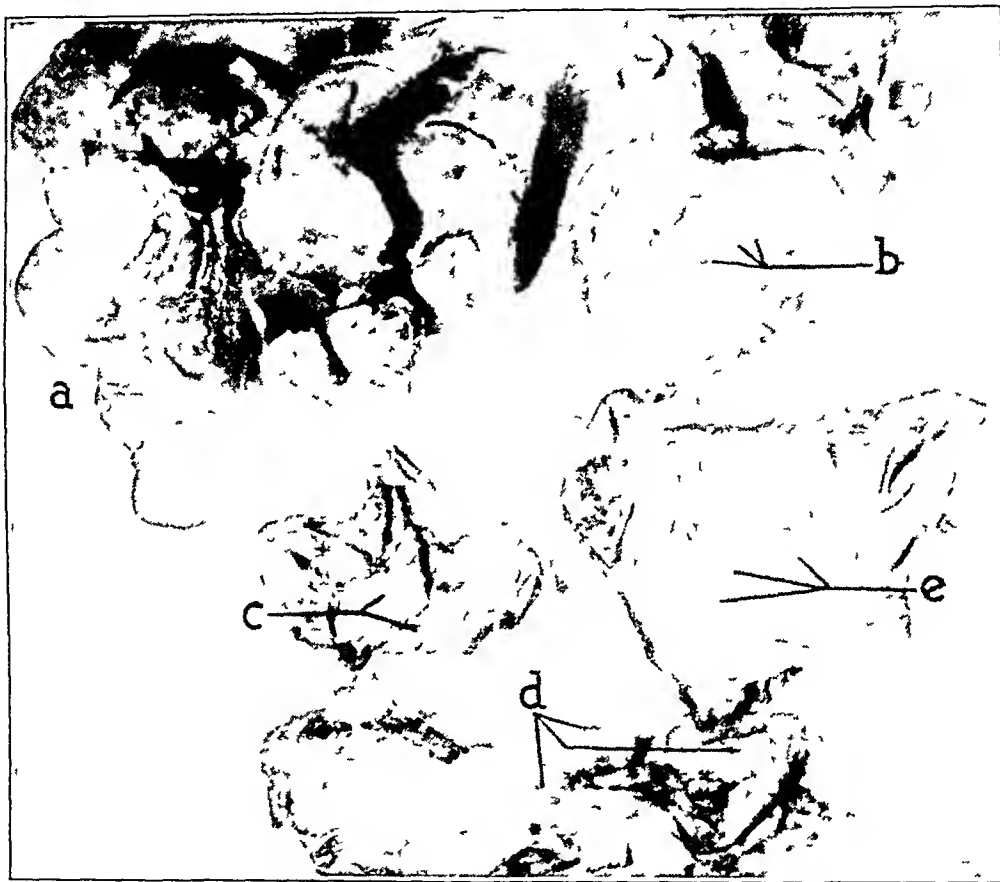


Fig 1—Gross specimens of (a) the right and left lungs, (b) heart and pericardium, (c and e) diaphragm and parietal peritoneum and (d) serosal surface of the left lung showed that the alveoli were filled with large epithelioid cells, varying the serous membranes.

The coronary arteries showed marked atheroma with sclerosis. There was no occlusion. The aorta showed slight atheromatous change (not syphilitic).

Both the visceral and the parietal pleura, to a more marked extent on the left side, showed numerous elevated, firm, grayish white nodules, 1 to 3 mm in diameter, in some instances extending into the pulmonary parenchyma.

In the left lung, in the lower portion of the upper lobe, there was a firm, almost completely consolidated area 8 to 9 cm in diameter, which grossly gave the appearance of a lobar pneumonic area during the stage of gray hepatization.

However, it was not moist, so that this grayish white, solidified area appeared to be a malignant growth. It did not lead directly into a bronchus, on gross examination.

The left bronchus, near its bifurcation, showed a firm, grayish white nodule, the size of a small pea, extending into the pulmonary tissue. This was evidently the site of primary bronchogenic carcinoma. The rest of the left lung was crepitant and showed moderate congestion and edema. No old or recent areas of tuberculosis were observed within the pulmonary tissue.

The right lung showed marked edema and slight congestion.

There was no free peritoneal fluid. The entire parietal peritoneum was studded with numerous gray, flattened nodules, 1 to 3 mm in diameter. Similar nodules were present on both surfaces of the diaphragm. These nodules in the peritoneal cavity were most numerous on the left parietal wall and extended into the pelvic peritoneum covering the serosa of the urinary bladder.

The cecum and ascending colon showed a few nodules, 1 or 2 mm in diameter, on the serosal surface. The lymph nodes were not enlarged.

The prostate showed slight hyperplasia. It was moderately firm but did not appear grossly to harbor a malignant growth.

The liver was slightly enlarged and showed moderate congestion. On the posterior portion of the left lobe, near the periphery, were two grayish yellow nodules, 3 and 6 mm, respectively, in diameter, showing slight central umbilication.

The gastrointestinal tract was normal. There was no ulceration or evidence of malignant growth. There were a few tiny malignant nodules on the serosa of the cecum.

The skull revealed no abnormality.

The spinal fluid was clear. There was cerebral edema, so that the convolutions were flattened. There was marked congestion of the veins on the surface of the brain. The pituitary body was grossly of normal size. The sella turcica was normal. The blood vessels appeared fibrotic. There was an area of recent softening in the right hemisphere. A small area which resembled a tubercle was observed in the cortex in the left upper parietal area. An area which also resembled tuberculoma was seen in the temporal lobe on the right side.

Histologic Postmortem Examination—Sections of the malignant growth in the left lung showed that the alveoli were filled with large epithelioid cells, varying markedly in size and exhibiting acinar formation. These cells contained large hyperchromatic nuclei, and many showed mitotic figures. Papillary arrangement of the cells was noted in other areas. The growth was a bronchogenic adenocarcinoma showing marked regressive changes.

Examination of the metastatic nodules in the pericardium, liver, peritoneum and other involved organs showed a striking resemblance to the original malignant growth in the left lung.

The gross examination of cut tissues of the brain showed highly stained metastatic nodules with a predilection for the cortex. There was no apparent involvement of the white matter. The diameter of the nodules varied from 0.5 mm or less to 6 mm. The larger nodules were observed in the motor cortex. Small metastatic nodules were seen throughout the cerebellum.

The meninges were thickened, and over the sulci the subarachnoid space contained a cellular exudate consisting of round cells and pigment-bearing histiocytes. At the periphery of one large nodule in the motor area there was seen for a considerable distance a single layer of epithelial cells occupying the position of the pia. This single layer, in all appearances, looked like the epithelial lining of a bronchus. From this single layer there were invaginations of the epithelial

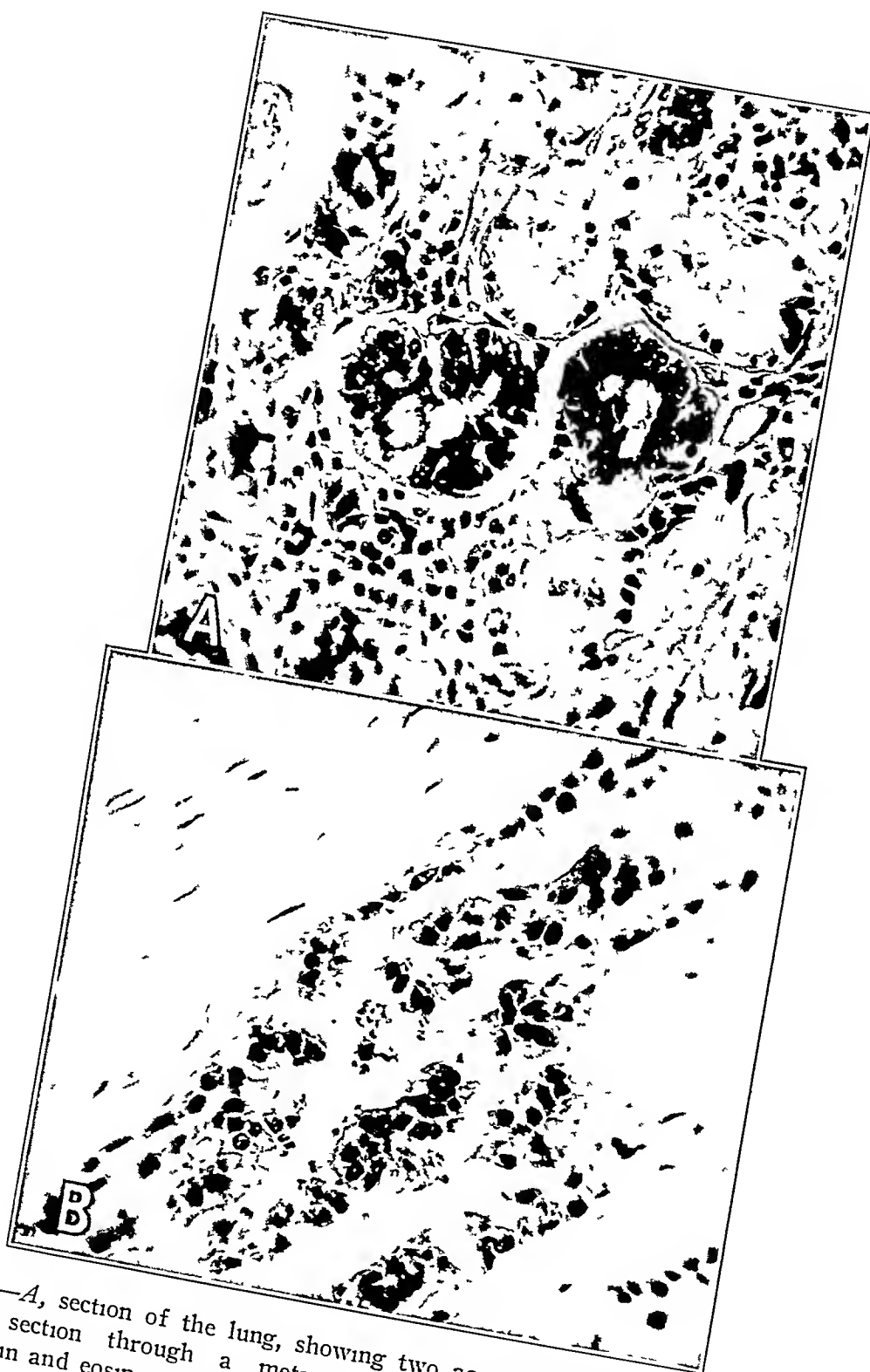


Fig 2—*A*, section of the lung, showing two acinar formations of malignant cells *B*, section through a metastatic nodule involving the pericardium
Hematoxylin and eosin stain, high power



Fig 3—*A*, section showing the division between the anterior and the posterior lobe, with the pars intermedia lying diagonally between the two lobes. The upper portion shows the metastatic involvement of the posterior lobe, low power. *B*, high power view of the metastatic cells in the posterior lobe, showing the character of the cells and their arrangement.



Fig 4—A a section (low power) through the cerebral cortex which includes the first, second and third layers showing complete absence of a normal cortical architecture. There is a single layer of metastatic carcinoma cells on the surface of the cortex with invaginations here and there simulating the epithelial lining and secretory glands of a bronchus. There are also groups of metastatic cells forming acini. B high power view of the boxed area in A showing the character of the metastatic cells. Several gitter cells can be seen in this section. Toluidine blue stain.

cells which extended into the lamina zonalis, producing what appeared to be glandular, tubular formations

The cells in the nodules were made up of deeply staining nuclei and cytoplasm and were arranged usually in a single layer in tubular or acinar formation. The cells were columnar, and others appeared to be flat squamous epithelial cells. In the cortex there were many compound granular cells in the areas invaded by these nodules. The cortical architecture showed a disturbance in the number of ganglion cells, with small areas devoid of normal cellular elements. The ganglion cells showed evidence of chronic disease. A moderate degree of marginal gliosis and increased gliosis of the cortex and subcortex were noted. Neuronophagia was present to a slight degree. The larger vessels showed metachromasia, involving the media in particular. There was no evidence of atheroma formation. The walls of the vessels of moderate and of small size presented hyalinization. The capillaries had a thickened endothelium and in the region of the metastatic nodules showed this to a marked degree.

In view of the clinical picture of diabetes insipidus, the question of the anatomic locations of the various lesions had to be considered. The entire posterior lobe of the pituitary body was completely destroyed as the result of invasion by carcinomatous tissue. Cells in this new tissue were arranged in places in acinous formation and in other places were without regular arrangement. The cells were frequently larger than the usual epithelial cell and occasionally contained large hyperchromatic nuclei, some of which were undergoing mitosis. While there was fairly sharp localization to the posterior lobe, at its connection with the anterior portion slight invasion into the glandular portion of the pituitary body was visible. For the most part the new growth was restrained within the capsule, but occasionally some of the tumor cells were seen in the capsule itself. The stalk of the pituitary body was filled with metastatic cells. A comparison of the tumor growth within the pituitary body with the original lesion in the lung and with metastasis to some of the other organs revealed a remarkable resemblance.

Serial sections of the hypothalamic region and the region of the third ventricle were carefully examined for evidences of tumor tissue. Microscopic islands of carcinoma were present in the entire cerebrum and cerebellum, including the meninges. The region of the third ventricle and of the supraoptic nuclei, however, was entirely free from carcinoma. There were comparatively recent hemorrhages in this area, but these, because of their recent origin, did not indicate any long-standing condition.

Diagnosis—The following diagnosis was made: parenchymatous degeneration of the heart, coronary atherosclerosis, primary bronchogenic carcinoma of the left lung, with metastasis to the pleura, diaphragm, peritoneum, pericardium, liver, brain and pituitary body, congestion and edema of the right lung, congestion of the spleen, chronic atrophic splenitis, nephrosclerosis, congestion of the kidneys, cloudy swelling, congestion and metastatic carcinoma of the liver, slight hyperplasia of the prostate, terminal petechial hemorrhages in the subthalamic region, cerebral arteriofibrosis, with chronic cell change, metastatic bronchogenic carcinoma of the brain, and metastatic involvement of the posterior lobe of the pituitary body and of the infundibulum.

COMMENT

This patient entered the hospital presenting only the symptoms of diabetes insipidus. The history, the physical examination and the

laboratory data gave no definitive clues as to the etiologic factor responsible for the disturbance in water metabolism. Examination of the chest revealed an area of bronchovesicular breathing on the left side at the seventh interspace posteriorly. This was confirmed by the roentgenographic findings, which, however, were interpreted as indicating inflammatory and not malignant involvement. There was no evidence of a malignant process from an a priori consideration. In cases in which a diagnosis of a malignant process has been definitely established, for instance, after operation for carcinoma of the breast or in cases in which an active malignant process has been conclusively demonstrated by biopsy or roentgenographically, and in which diabetes insipidus has supervened, the conclusion is warranted, as Fink⁶ has maintained, that the supraopticohypophyseal system has been involved. Conversely, on the basis of our case, diabetes insipidus may be considered as the manifestation of a metastatic involvement of the supraopticohypophyseal system secondary to an undetermined primary malignant growth elsewhere, which should be definitely ascertained by the clinician or ruled out as one of the etiologic factors producing the diabetes insipidus.

The assumption of a primary lesion elsewhere and its early apprehension are obviously important as regards therapy. Boyd¹⁴ has stated

Lung tumors tend to spread and the secondary growths may be the first announcement that there is anything wrong with the patient. Spread is three-fold (1) through the lung, (2) to the lymph nodes, and (3) to distant organs. Spread to distant organs is very common. The order of frequency is as follows: (1) liver, (2) brain and bone, (3) kidney and adrenal, less commonly the pancreas, thyroid, etc., may be involved. The brain metastasis is often mistaken clinically for a primary cerebral tumor, because the cerebral symptoms may precede the pulmonary ones.

In addition to the amelioration of the polyuria by the use of solution of posterior pituitary, more lasting benefit may be expected by irradiation of the metastatic lesion involving the hypothalamohypophyseal area, as well as appropriate attention to the primary malignant growth. Desbuquois¹⁵ reported a case of cervical malignant lymphogranulomatosis in which the growth receded for a period of one year after irradiation of the involved glands, only to be followed with a recurrence complicated by diabetes insipidus. Roentgen treatment of the cervical lymph nodes and of the pituitary and hypothalamic region resulted in marked amelioration of symptoms, the urinary output decreased from 12 to 13 liters per twenty-four hours previous to irradiation to about 2 liters after irradiation.

14 Boyd, W. Textbook of Pathology, ed 2, Philadelphia, Lea & Febiger, 1934, pp 484-486.

15 Desbuquois, M. B. Sur un cas de lymphogranulomatose maligne compliquee de diabete insipide, Arch med-chir de Province 26 25, 1936.

The gross appearance of the metastatic nodules involving the pleura, parietal pericardium and serous membranes of the abdominal cavity was not unlike that of miliary tubercles, indeed, on macroscopic inspection the nodules in the cerebrum and cerebellum were first thought to be tubercles. The histologic examination showed them to consist of malignant cells similar morphologically to those of the primary bronchogenic carcinoma. According to Karsner,¹⁶ miliary carcinosis manifests itself by innumerable nodules, a few millimeters in diameter, that are translucent and white, that bulge in the cut surface and that usually are situated along the course of the lymphatic vessels.

The metastatic invasion of the brain in our case was most likely hematogenous. Winkelman and Eckel,¹⁷ in discussing the various modes of dissemination of carcinoma to the nervous system, enumerated the adherents to the theories of lymphogenous and of hematogenous dissemination, or both, and of spread by direct extension. They concluded, however, that metastasis from distant parts (thoracic and abdominal organs) can be best explained by assuming that the blood stream acts as the channel of transmission to the brain. They substantiated their claim by citing a case of primary carcinoma of the breast in which cancer cells were found within the blood vessels of the brain.

In view of the reports in the literature of the hypothalamic origin of diabetes insipidus, careful study of this region was carried out, but no evidence of metastasis could be found. There were recent capillary hemorrhages in the ventromedial hypothalamic nuclei which, however, were terminal in nature. The entire posterior lobe of the pituitary body and the infundibulum were filled with metastatic carcinoma, part of the capsule and a minute portion of the anterior lobe of the pituitary body were also invaded. The polyuria in this case, therefore, was due to infundibulohypophyseal involvement alone.

SUMMARY AND CONCLUSION

A case of diabetes insipidus in which the history and clinical study failed to reveal the etiologic factor is presented.

Postmortem study showed primary bronchogenic carcinoma involving the left lung, with metastasis to the serous membranes of the thoracic and abdominal organs and to the cerebrum, cerebellum, hypophysis and infundibulum, with sparing of the hypothalamus.

16 Karsner, H. T. Human Pathology, Philadelphia, J. B. Lippincott Company, 1926, pp. 581-582.

17 Winkelman, N. W., and Eckel, J. L. Metastatic Carcinoma of the Central Nervous System, *J. Nerv. & Ment. Dis.* **66**: 1 and 133, 1927.

In the absence of conclusive evidence as to the etiologic factor in a case of diabetes insipidus, it is suggested that a masked malignant process be suspected, that an effort be made to establish the primary source and that, on an empiric basis, irradiation be given to the hypothalamohypophyseal area

Dr N W Winkelman made the neuropathologic study

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CHEMICAL FACTORS CONCERNED IN THE FORMATION OF GALLSTONES

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It is well known that in certain of the domestic animals, notably dogs, sheep, cats and rabbits, gallstones rarely form spontaneously and cannot be produced experimentally. Schlotthauer and Stalker¹ reported the occurrence of bilirubin stones in 2 of 155 dogs studied at autopsy. Ivy² has observed bilirubin stones in only 1 of 500 dogs whose gallbladders were opened routinely. Approximately 150 dogs were used during the course of our experiments, and calculi were never observed. The spontaneous occurrence of true cholesterol stones in dogs, sheep, cats and rabbits has not been reported. In contradistinction to these animals are certain others—chiefly human beings, oxen and hogs—in which biliary calculi occur frequently. A satisfactory explanation of the differences in the bile of these two groups of animals would do much toward accounting for some of the factors concerned in the production of gallstones.

In 1903 Harley and Barratt³ reported a series of observations in which gallstones from human beings placed in the gallbladders of dogs dissolved over varying periods. These results confirmed the original observations made by Labes⁴ a few years previously. Since the original reports, numerous other workers⁵ have obtained similar findings. In

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1 Schlotthauer, C. F., and Stalker, L. K. Cholelithiasis in Dogs, *J. Am. Vet. M. A.* **41** 758, 1936

2 Ivy, A. C. Personal communication to the authors

3 Harley, V., and Barratt, W. An Experimental Enquiry into the Formation of Gallstones, *J. Physiol.* **29** 341, 1903

4 Labes, cited by Brockbank, E. M. On Gallstones, Philadelphia, P. Blakiston's Son & Co., 1896, p. 67

5 Naunyn, B. A Treatise on Cholelithiasis, translated by A. E. Gairod, London, New Sydenham Society, 1896. Frerichs, F. T. *Klinik der Leberkrankheiten*, Braunschweig, F. Vieweg & Sohn, 1861, vol. 2, p. 487. von Hause-

1930 Walsh and Ivy⁶ determined the rates of dissolution of human gallstones in a large series of dogs under varying conditions. They concluded that the rate of solution of a human gallstone in the dog's gallbladder is not significantly altered from the normal by feeding high fat, high cholesterol diets. A slight increase in the rate of solution was reported on the addition of bile salts and cod liver oil to the diet. They further observed that factors which diminished the flow of bile into and out of the gallbladder or which diminished the concentrating power of the wall of the gallbladder, as when cholecystitis with fibrosis was produced, decreased the rate of solution. In an effort to determine the essential differences between dog and human bile which would account for the solvent capacity of dog bile, additional studies showed that the greatest difference between human and dog bile was in the ratio of the nonsaponifiable (cholesterol) to the saponifiable (fats and fatty acids) substances in the bile. The concentration of saponifiable material in relation to the nonsaponifiable material was found to be relatively low in human bile but very high in dog bile. They concluded that the solubility of cholesterol in bile depends on the activity of the bile salts or bile acids in holding the fats and fatty acids in aqueous solution or in combining with them to form soaps at the acid p_H of the gallbladder.

This report presents additional evidence in support of this hypothesis. We have of necessity repeated a considerable amount of the work reported by Walsh and Ivy but have extended it, using improved methods in an effort to clarify the problem further.

In a previous study we⁷ reported the results of treatment in 65 cases of chronic cholecystitis with and without calculi by measures which were designed to increase the free flow of bile. Marked subjective improvement was observed in those patients who received frequent feedings of milk and cream up to the point of tolerance to induce physiologically the contraction and evacuation of the gallbladder and

mann, D. Die Lösungsmöglichkeit der Gallensteine, *Virchows Arch f path Anat* **212** 139, 1913. Leon, H. Die gallensteinlösende Wirkung des Karlsbaderwassers, *Deutsche med Wchnschr* **40** 786, 1914. Glaessner, K. Ueber die Resorption der Gallensteine, *Wien klin Wchnschr* **31** 549, 1918. Wilhelm, R. Zur Lösungsvermögen der Galle gegenüber Cholesterensteinen, *ibid* **31** 696, 1918. Harrison, F. M., and Barber, W. H. Effect of Living Gallbladder on Human Biliary Calculi, *Proc Soc Exper Biol & Med* **25** 226, 1927. Mirolli, A. La ipertrofia e la iperplasia della tonaca muscolare della coleciste nelle colecistiti, *Arch ital di chir* **30** 314, 1931.

6 Walsh, E. L., and Ivy, A. C. Observations on the Etiology of Gallstones, *Ann Int Med* **4** 134, 1930.

7 Brown, C. F. G., and Dolkart, R. E. Ketocholanic Acids in the Medical Management of Low Grade Gallbladder Disease, *J A M A* **108** 458 (Feb 6) 1937.

ketocholelanic acids to stimulate directly the flow of hepatic bile, together with antispasmodic medication to decrease the hypertonicity of the biliary and gastro-intestinal tracts which generally accompanies cholecystitis. Concomitant with the relief of the subjective manifestations of the disease, definite roentgenologic improvement of the function of the gallbladder was noted in a large percentage of cases. Since the first report, 55 additional patients have been given this form of treatment.⁸ The results for this group confirm our previous findings.

In view of the clinical improvement in patients with disease of the gallbladder noted with medical management to prevent biliary stasis and to promote emptying of the biliary passages, it was desired to determine the exact extent of the increase in bile flow obtained by the oral administration of oxidized bile acids.

TABLE 1—*Choleretic Action of Mixed Ketocholelanic Acids on Oral Administration to Dogs with a Chronic Biliary Fistula**

Experiment Number	Control Period		Test Period		Percentage of Increase
	Days	Average Daily Output of Bile, Cc	Days	Average Daily Output of Bile, Cc	
1	4	86	4	109	26.7
2	6	100	5	142	42.0
3	4	57	4	80	40.3
4	5	93	11	104	11.8
5	4	81	4	119	46.9
6†	14	405	6	457	19.3

* The dose was 22.5 grains (1.5 Gm.) per day.

† In experiments 1 to 5 the animals were sham feeding dogs with a biliary fistula, prepared according to the method of Kocour and Ivy. Dog 6 was prepared by the same method but was not a sham feeding dog. It differed from the 5 others, however, in that it was maintained with constant suction on the tube in the common bile duct. All the dogs had a constant intake of food and fluid during the control and test periods. Bile was returned to each of the animals through a tube into the jejunum in constant amount during the control and test periods.

For this purpose dogs with biliary fistulas were prepared,⁹ a modified Rous-McMaster procedure being used after the gallbladder had been removed. In order to maintain the animals in as normal a physiologic state as possible, provision to return part of the bile collected through the fistula was made by the insertion of a catheter into the jejunum. Four dogs with a chronic biliary fistula were used in the experiments. The results are shown in table 1. All the animals were maintained on a constant intake of food and fluid during the periods of observation. The amount of bile returned during the control and test periods was constant for all the animals. In experiment 6 constant suction was maintained in the tube leading into the common duct during the control and test periods, after the method described by Kocour and Ivy.¹⁰

8 Mock, H. E., Brown, C. F. G., and Dolkart, R. E. The Conservative Treatment of Gallbladder Disease, Surg., Gynec. & Obst. 66:79, 1938.

9 Dr. E. J. Kocour prepared these dogs, and F. W. Gorham assisted with the experiments.

10 Kocour, E. J., and Ivy, A. C. To be published, personal communication to the authors.

The intravenous action of oxidized bile acids has been studied by numerous investigators,¹¹ but there have been few reports of the degree of choleresis which is obtained with oral administration. It was observed that the oral administration of oxidized or ketobile acids¹² produced consistent choleresis, increasing the bile flow from 11.8 to 46.9 per cent. The intravenous action of mixed oxidized bile acids (3,7,12-triketocholanic, 3,7-diketocholanic, 3,12-diketocholanic and 3-ketocholanic acid) was found to be more marked, as would be expected. Injection of 7 to 50 mg per kilogram of body weight to dogs with an acute biliary fistula was found to increase the bile flow from 53.5 to 278.1 per cent. Injection of 250 mg per kilogram of body weight resulted in an increase of 457.6 per cent in the bile flow.

In view of previous observations of the dissolution of the human gallstone when placed in the gallbladder of the dog, we wished to determine next whether the normal rate of dissolution in the dog could be altered by placing the animal on a regimen to increase the flow of bile similar to that received by the series of patients under our observation.

Through an abdominal incision a stab wound was made in the fundus of the gallbladder after aspiration of the bile contained therein. A human gallstone, that had been weighed, was then inserted, and the opening was closed with a purse string suture. After an interval of sixty-five days each dog was killed, the cystic duct was ligated and the gallbladder was removed. The stones or fragments thereof were again weighed, and the loss of weight was determined. Eighty-eight dogs were used in the experiments, 76 of which survived the duration of the sixty-five day period of observation. For statistical and comparative purposes the animals were divided into three groups. For the first series of animals (14 controls and 20 treated animals) a miscellaneous assortment of gallstones obtained from the gallbladders of various human beings was used. For the second group of animals (10 controls and 21 treated animals) human gallstones were used which were obtained from one gallbladder. For the 11 animals in group 3, stones obtained from one gallbladder were used. In groups 2 and 3 we attempted to eliminate from the experiment the variable due to differences in gallstones obtained from different gallbladders, assuming that stones obtained from one gallbladder are of similar character. Table 2 shows the results of these experiments.

It will be observed that in the first group of animals, in which miscellaneous stones were used (group 1, A and B), a considerable increase in the rate of dissolution occurred in the dogs which received ketocholanic acids to increase the biliary flow. When we attempted to repeat this experiment under conditions that were better controlled, that is, by

11 Neubauer, E. Dehydrocholsäure, eine wirksame ungiftige Glied der Gallensäuregruppe, *Klin Wchnschr* 2 1065, 1923. Adler, A., and Schmid, E. Diagnostische und therapeutische Verwendbarkeit der Gallensäure der Leber und Gallenblase, *Fortschr d Therap* 1 733, 1925.

12 Ketochol was used, being supplied by G. D. Searle & Co., Chicago.

elimination of the variable due to the use of miscellaneous stones (group 2, A and B), we were unable to confirm our previous results

However, the material used in these two sets of experiments differed, in that that used in the second set had been further processed and purified and a residue of impure material had been removed. When the second set of experiments (group 2, A and B), in which stones from one gallbladder were used, failed to confirm the original findings, it was at first thought possible that the change in the purity of the ketocholanic acids might have had some bearing on the results. In an effort to check this possibility an additional group of animals (group

TABLE 2—*Composite Table of the Results of Solution of Human Gallstones in the Gallbladder of the Dog*

Type of Stone	Number of Dogs	Treatment	Average Original Weight, Gm	Average Final Weight, Gm	Average Loss of Weight, Gm	Average Loss, %	Probable Error
Group 1							
A Mice	14	Controls, given stock diet only	0.316	0.095	0.209	73.3	± 5.610
B Mice	20	Stock diet plus 22.5 grains (1.5 Gm) of ketocholanic acid daily	0.281	0.008	0.278	98.0	± 0.014
Group 2							
A MR1	10	Controls, given stock diet only	0.486	0.075	0.410	83.7	± 2.530
B MR1	10	Stock diet plus 22.5 grains (1.5 Gm) of ketocholanic acid daily	0.488	0.086	0.402	83.5	± 2.540
C MR1	6	Stock diet plus 33.75 grains (2.2 Gm) of ketocholanic acid daily	0.355	0.061	0.311	82.9	± 4.030
D MR1	5	Stock diet plus 30 grains (2 Gm) of ketocholanic acid residue daily	0.325	0.028	0.297	91.3	± 1.960
Group 3							
A W	6	Controls, given stock diet only	0.426	0.078	0.354	83.6	± 5.190
B W	5	Diet high unsaturated fat 3 times daily, high in protein, high in tryptophan, plus 33.75 grains (2.2 Gm) of ketocholanic acid daily	0.323	0.006	0.317	98.5	± 0.607

* The duration of the period of observation was sixty-five days

2, C) were given a sample of unpurified ketocholanic acids prepared exactly as for the animals in group 1. In addition, another group of 5 animals (group 2, D) were given an equivalent quantity of the impure residue in place of the ketocholanic acids. It will be observed that in no instance was there any significant alteration from the normal rate of dissolution.

With the third group of animals we made an effort to bring about the interaction of several factors, all of which should theoretically have a definite effect in influencing the rate of dissolution of the gallstones. The first factor in the therapy was designed to increase the flow of bile. For this purpose the animals received linseed oil three times daily, because of the well established observations that fat in the duodenum causes evacuation of the gallbladder. Linseed oil was chosen because

the effect of an unsaturated fat was desired. In addition, the animals received ketocholanic acids by mouth to stimulate the increased production of bile by the liver.

The second factor in the therapy was an effort to increase the production of bile salts by bringing certain metabolic factors into play. Whipple and his co-workers¹³ have shown that in dogs the output of bile salt is fairly constant with uniform dietary conditions. Fasting was found to reduce the output of bile salts to low levels. Smith and Whipple¹⁴ in further studies demonstrated that meat or meat products fed to dogs with a biliary fistula resulted in an increased production of whole bile and a twofold to threefold increase in the output of bile salts. In attempting to ascertain the essential factor in food protein, further feeding experiments were carried out, gelatin being used as the basic protein.¹⁵ They found that gelatin feeding supplemented by the addition of tryptophan produced a sustained rise in the output of bile salts.

The animals of group 3 in our experiments were given, therefore, in addition to a regimen to increase the flow of bile, a diet which was high in protein and high in tryptophan in an effort to increase the production of bile salts, as suggested by Whipple. Although the table shows there was an increase of approximately 15 per cent in the rate of dissolution of the stones in the treated dogs, we do not consider this to be statistically significant in view of the probable error of the experiment. Three of the control dogs showed 90 per cent or greater dissolution, and the remaining 3 controls brought the average down to 83.6 per cent.

These results show that no significant difference could be demonstrated in the rate with which dogs normally dissolve human gallstones, despite several variations in therapy. Our findings are much in agreement with those reported by Walsh and Ivy, although they suggest that slightly increased dissolution was obtained by the addition of bile salts and cod liver oil to the diet. Two possible conclusions may be drawn. First, either the therapy was ineffective in achieving any significant alteration of the constituents of the bile or an increase of the flow of bile is not a pertinent factor to increasing the rate of dissolution. The second possible conclusion is that in the normal dog the bile in the gallbladder is of such solvent character that it works at optimum capacity and is

13 Smith, D. P., Groth, A. H., and Whipple, G. H. Bile Salt Metabolism I. Control Diets, Methods, and Fasting Output, *J. Biol. Chem.* **80** 659, 1928.

14 Smith, H. P., and Whipple, G. H. Bile Salt Metabolism II. Influence of Meat and Meat Extractives, Liver and Kidney, Egg Yolk and Yeast in the Diet, *J. Biol. Chem.* **80** 671, 1928.

15 Whipple, G. H., and Smith, H. P. Bile Salt Metabolism III. Tryptophane, Tyrosine, and Related Substances as Influencing Bile Salt Output, *J. Biol. Chem.* **80** 685, 1928.

consequently not affected by therapy. In the light of the studies of Walsh and Ivy, we believed the latter to be more probable.

We wished to determine next whether there is any essential difference in the stone-solvent properties of the bile in the gallbladder of the group of animals which form gallstones spontaneously and of animals in which they do not occur. If there was a difference in stone-solvent properties of the bile of these animals, we wished to determine which fraction of the bile was responsible and whether this could be correlated in any way with the great solvent capacity of dog bile.

The first factor to be studied in this connection was the role of the p_H of the bile. To carry on these investigations we performed *in vitro* experiments, using in general the procedure described by Walsh and Ivy.

Human gallstones, similar in character and obtained from one gallbladder, were weighed, wrapped in gauze to prevent mechanical injury and suspended in flasks to which was added either acid or alkaline bile. These flasks were then placed in a mechanical shaking device operating at a speed of 25 to 30 half revolutions per minute. The stones were shaken continuously for seven days in a constant temperature chamber at 39 C. Seventy experiments were carried out with human, dog and ox bile which had been buffered to maintain a p_H of 4.5 to 5 for half of the experiments and a p_H of 8.4 to 9 for the other half. Other studies were carried out in which the p_H of the bile in the gallbladder of the dog was measured at the time of the insertion of a human gallstone and sixty-five days later, when the stone was removed.

No statistically significant difference was observed in the relative solvent action of acid and of alkaline bile from the ox, the dog and man on human gallstones of the mixed cholesterol variety¹⁶. These findings were not in agreement with the conclusions drawn by Feldman, Morrison and Krantz from their observations that the human gallstone dissolved in the gallbladder of the dog, which was an acid bile, but did not dissolve in the gallbladder of the guinea pig, which has an alkaline bile¹⁷. They concluded that the p_H of the bile is the important factor in determining whether or not a human gallstone will dissolve in an animal's gallbladder. On the basis of our studies and the examination of their data, we believe their conclusions to be unwarranted.

Other experiments were carried out *in vitro* by the technic described, in which solutions of bile salts were used as the mediums in which the gallstones were shaken. Table 3 shows the results of these miscellaneous experiments. In the course of these studies in shaking human gallstones, it was observed that there were certain experimental diffi-

16 Dolkart, R. E., Jones, K. K., and Brown, C. F. G. The Relation of the Hydrogen Ion Concentration of Bile to the Formation of Gallstones, *Am J Digest Dis & Nutrition* 4: 587, 1937.

17 Feldman, M., Morrison, S., and Krantz, J. C. Etiology of Gallstones, *Am J Digest Dis & Nutrition* 4: 13, 1937.

culties In the first place, it was difficult to obtain a sufficient number of human gallstones from one gallbladder to make an adequate number of comparative experiments In the second place, there was considerable variation in the size and in the weight of the stones obtained from the same gallbladder, so that there was no constancy of surface area in contact with the dissolving solution In the third place, it was believed that even though stones were obtained from the same human gallbladder there was no assurance that they were of exactly the same composition, in which case the number of experimental variables would be further increased To overcome these difficulties, four thousand human gall-

TABLE 3—Composite Table of Results of Shaking Human Gallstones *in Vitro* at 39 C at Twenty-Five to Thirty Half Revolutions per Minute for Seven Days*

Solution Used	Stones A		Stones B		Stones C		Stones D	
	No of Exper	Loss of Weight, %	No of Exper	Loss of Weight, %	No of Exper	Loss of Weight, %	No of Exper	Loss of Weight, %
1% solution of sodium glycocholate in 5% sodium carbonate	17	-4.34 ± 0.985	25	-5.52 ± 0.177			12	-5.20 ± 0.395
1% solution of sodium salts of mixed keto cholic acids, pH 8.3	24	-2.01 ± 0.553	10	-2.67 ± 0.072	20	-3.82 ± 0.728	8	-2.88 ± 1.605
1% solution of mixed keto cholic acids in 5% sodium carbonate	30	-7.67 ± 0.072	30	-2.91 ± 0.170	16	-3.45 ± 0.480	4	-3.80 ± 0.548
1% solution of bile salts, fatty acid residue †	12	-2.73 ± 0.140	10	-0.72 ± 0.053			8	-1.84 ± 1.221
1% solution of iron bile salts, mixture	5	-11.29 ± 0.799	5	-6.15 ± 0.219				
Distilled water, control	12	-0.20 ± 0.096	10	-0.73 ± 0.066			12	-0.51 ± 0.609

* The gallbladders from which the stones were obtained are designated by letters A, B, C and D

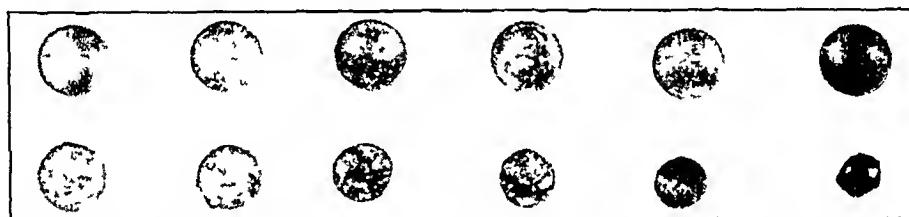
† See the discussion of the methods and materials

stones of mixed variety were collected These stones had been removed either at operation or at autopsy, and were prepared as follows

The stones were pulverized, the powder was thoroughly mixed and the material was run through a pharmaceutical tablet press under considerable pressure It was found that the pulverized material had adequate cohesive power, and the addition of starch or other binders was unnecessary The gallstone tablets thus obtained were of uniform size, density and composition The variations in weight between a large number of tablets was extremely small Analysis of the tablets showed them to contain 70.6 per cent cholesterol Eighteen hundred and forty comparative experiments were performed with the standardized gallstone tablets prepared by this method Twenty tablets were shaken separately in each of the solutions indicated in the accompanying tables, the average loss of weight was determined and the probable error was computed The accompanying figure shows the tablets which were not shaken as compared with tablets in various stages of dissolution after shaking

Owing to the fact that the gallstone tablets were prepared from the mixed variety of human gallstones, it would be theoretically possible for the various solutions employed to dissolve out the noncholesterol components. We checked this factor by determining the cholesterol content of the tablets and by comparing these figures with those obtained for tablets which were not shaken. The results showed that most of the losses in weight in each case could be accounted for by the decrease in the cholesterol content. The question may well arise at this point as to whether the cholesterol actually went into solution or whether it was merely dispersed in the shaking solutions. From our data it appears that the former was the case. We are, however, studying this phenomenon further in another group of experiments.

In attempting to determine the factors concerned in the dissolution of cholesterol gallstones in animal bile, the bile obtained from the ox and the hog, animals which form gallstones, was compared with the bile obtained from the sheep and the dog, animals which do not form gallstones. Table 4 shows that undiluted bile from the gallbladder of each of



The top row of gallstone tablets have not been shaken. The bottom row of tablets have been shaken and dried and are in various stages of dissolution.

these animals had a definite solvent capacity under the uniform conditions of the experiments. Dilution with distilled water resulted either in a total loss or in a marked reduction of the solvent power. A fresh portion of the bile from each of these animals was then extracted with an equal volume of 95 per cent alcohol, which separated it into two fractions. The alcohol-insoluble fraction was filtered out, the alcohol evaporated off and the residuum taken up in distilled water in the concentrations indicated in the table. In no instance did the alcohol-insoluble fraction, consisting chiefly of protein, mucin and inorganic salts, manifest any significant dissolving power.

Shaking experiments were next carried out, the alcohol-soluble fractions being used as the shaking mediums. Before the stones were shaken in these fractions, the alcohol was evaporated off, and by the addition of distilled water, the remaining alcohol-soluble material was brought to a concentration equivalent to that in which it occurred in the bile. Stones shaken in this fraction showed considerable dissolution. In some instances this was either equal to or greater than the dissolution

occurring in the undiluted whole bile. When the alcohol-soluble fraction was saponified, two more bile fractions were obtained. The nonsaponifiable fraction, consisting of approximately 80 per cent cholesterol, was found to be so highly insoluble that it could not be used as a medium in which to carry out shaking experiments. When stones were shaken in the saponifiable or fatty acid fraction, however, the solvent power was found to be either quantitatively equal to or greater than that of undiluted bile.

On the basis of these findings it appears that the solvent capacity of bile can be isolated in the saponifiable or fatty acid fraction. We wished to determine next whether there was any correlation between the

TABLE 4—*Dissolution of Standardized Gallstone Tablets Made from Human Gallstones in Various Fractions of Animal Bile**

Bile Fraction	Ox Gallbladder Bile, %	Hog Gallbladder Bile, %	Sheep Gallbladder Bile, %	Dog Gallbladder Bile, %
Undiluted bile	-7.50 ± 0.371	-7.87 ± 0.133	-5.29 ± 0.467	-11.20 ± 0.143
Bile diluted 1:5 with distilled water	-0.07 ± 0.094	-4.24 ± 0.105	-2.82 ± 0.368	
Bile diluted 1:10 with distilled water	-0.07 ± 0.145	-2.75 ± 0.095	-2.30 ± 0.152	
Alcohol-insoluble fraction, equivalent to normal concentration	$+0.81 \pm 0.320$	-1.48 ± 0.068	-0.26 ± 0.168	-3.30 ± 0.212
Alcohol-insoluble fraction, concentrated 5 times	-1.20 ± 0.341	-3.68 ± 0.155	-2.14 ± 0.200	
Alcohol-soluble fraction, equivalent to normal concentration	-4.87 ± 0.200	-8.79 ± 0.324	-8.79 ± 0.525	
Alcohol-soluble saponifiable fraction, equivalent to normal concentration	-7.17 ± 0.276	-12.41 ± 0.302	-9.80 ± 0.196	-15.20 ± 0.254

* Each figure represents the average percentage of loss of weight for twenty experiments made simultaneously, with the probable errors determined. All the experiments show the result of one week of shaking at 25 to 30 half revolutions per minute at 39°C.

relative amounts of saponifiable material present in the bile of these animals. Table 5 shows the result of the analyses performed on samples of the animal biles used in the shaking experiments. It will be observed that the relative ratio of saponifiable to nonsaponifiable material was very high for the dog and the sheep but low for the ox and the hog. Other analyses of bile from human gallbladders showed that this ratio was even lower (1:5:1) than that found for these two species of stone-forming domestic animals.

In view of these observations, confirming the findings of Walsh and Ivy and of the numerous reports in the literature which ascribe the chief role in maintaining cholesterol in solution to the bile salts and bile acids, an additional group of shaking experiments were made in which the relative solvent action of various bile salts could be compared with that of fatty acids on an equitable basis. These results are shown in table 6 and will be discussed further. It should be noted at this point,

however, that in no instance did the solvent action of any of the bile salts approach that of any of the fatty acids used in the experiments

TABLE 5—*Quantitative Analyses of Animal Biles* Used for Fractionating Experiments†*

Determination	Ox Gallbladder Bile, Gm per 10 Ce	Hog Gallbladder Bile, Gm per 10 Ce	Sheep Gallbladder Bile, Gm per 10 Ce	Dog Gallbladder Bile, Gm per 10 Ce
Total solids	1 2760	1 5600	1 2490	2 5520
Total ash	0 1335	0 0790	0 1120	0 0976
Alcohol insoluble material	0 0350	0 1793	0 0370	0 1930
Nonsaponifiable fraction	0 0100	0 0190	0 0060	0 0142
Cholesterol	0 0080	0 0100	0 0045	0 0113
Saponifiable fraction	0 0630	0 1080	0 0778	0 2350
Bile salts, determined as chohe acid‡		0 0600	0 3100	1 1500
Ratio saponifiable to nonsaponifiable fraction	6 3 1	5 6 1	12 9 1	20 3 1

* All the samples were of summer bile. The analyses for ox bile were made on an aliquot sample from 5 gallons of fresh beef bile obtained from the stockyards. The analyses for hog bile were made on an aliquot sample from 3 gallons of fresh hog bile obtained from the stockyards. The analyses for sheep bile were made on an aliquot sample of 2 gallons of fresh sheep bile obtained from the stockyards. At 30 cc of bile per sheep, which is the average content of the sheep gallbladder, this represents the bile of 253 sheep. The dog bile was obtained from a large number of laboratory animals.

† All the figures represent analyses of 10 cc samples, with all determinations in duplicate.

‡ Method of Reinhold and Wilson (J Biol Chem 96 637, 1932)

TABLE 6—*Dissolution of Standardized Gallstone Tablets Made from Human Gallstones in Various Solutions of Bile Salts and Fatty Acids*

Solution	Percentage with 1% Concentration	Percentage with 5% Concentration	Percentage with 10% Concentration
Sodium glycocholate	— 2 99 ± 0 074	— 9 60 ± 0 341	—17 50 ± 0 415
Sodium taurocholate	— 3 00 ± 0 138	—12 30 ± 0 216	—22 30 ± 0 419
Sodium cholate	— 5 10 ± 0 110	—19 90 ± 0 482	—34 50 ± 0 526
Sodium desoxycholate	— 2 80 ± 0 071	—19 10 ± 0 488	—18 60 ± 0 381
Mixed bile salts (Wilson)	— 4 90 ± 0 154	— 7 71 ± 0 147	—15 70 ± 0 890
Bile salts mixture with Iron (Lilly)	— 4 10 ± 0 093	— 5 20 ± 0 119	— 8 30 ± 0 219
Sodium dehydrocholate (sodium salt of 3, 7, 12 triketocholanic acid)	— 0 34 ± 0 040	— 1 47 ± 0 097	— 2 69 ± 0 094
Sodium dehydrodesoxycholate (sodium salt of 3, 12 diketocholanic acid)	— 2 18 ± 0 067	— 3 69 ± 0 127	— 4 99 ± 0 148
Mixed ketocholanic acids (Searle)	— 5 80 ± 0 161	—10 32 ± 0 154	—11 52 ± 0 080
5% sodium carbonate, control		— 0 66 ± 0 305	
Sodium linoleate, 39 C	—11 24 ± 0 283	—16 62 ± 0 460	—20 78 ± 0 473
Sodium oleate, 39 C	—22 50 ± 0 499	—36 50 ± 0 455	—49 00 ± 0 469
Sodium oleate, 70 C	—33 80 ± 0 422	—64 60 ± 0 718	—76 50 ± 1 070
Sodium laurate, 70 C	—52 10 ± 0 325	—67 85 ± 1 032	—100 00 ± 0 000
Sodium stearate, 70 C	—32 40 ± 1 120	—48 60 ± 1 310	—57 60 ± 1 201
Sodium myristate, 70 C	—48 60 ± 0 938	—71 10 ± 0 880	
Sodium palmitate, 70 C	—13 10 ± 0 303	—53 40 ± 0 654	—62 20 ± 0 519
Sodium lauryl sulfonate, —39 C	—27 30 ± 0 269	—31 83 ± 0 796	—32 42 ± 0 151
Leecithin in water, —39 C	— 1 64 ± 0 077	— 1 06 ± 0 103	

* Each figure represents the average percentage of loss of weight in twenty experiments made simultaneously, with the probable errors determined. All the experiments are the results of 1 week of shaking at 25 to 30 half revolutions per minute at 39 C. Some of the experiments were made at a temperature of 70 C and are so indicated. All bile salts and bile acids were dissolved in a 5 per cent solution of sodium carbonate, fatty acids in sodium hydroxide added in sufficient amount to bring the pH of the solution to 8.3.

In comparing the relative activity of the various bile salts used, on first inspection it appeared that perhaps the reason sodium cholate

showed the greatest solvent capacity was that the solutions used were prepared as percentage concentrations rather than as molar solutions. Recalculation of the data on the basis of the relative molar concentrations, however, showed that there was no correlation.

Table 7 shows the relative action of the solutions containing both bile salts and fatty acids, each in 5 per cent concentration. It will be

TABLE 7—*Dissolution of Standardized Gallstone Tablets Made from Human Gallstones in Solutions Containing 5 per Cent Sodium Glycocholate Mixed with 5 per Cent Fatty Acids as Soaps (pH 8.3)*

Solution	Temperature, C	Dissolution, %	Percentage of Dissolution, Only the Soap (5%) Being Used	Percentage of Dissolution, Only the Bile Salt (5%) Being Used
Sodium laurate and sodium glycocholate	70	-53.35 ± 0.377	-67.85 ± 1.032	-9.61 ± 0.182
Sodium palmitate and sodium glycocholate	70	-48.00 ± 0.512	-53.40 ± 0.654	-9.61 ± 0.182
Sodium stearate and sodium glycocholate	70	-41.92 ± 0.209	-48.60 ± 1.310	-9.61 ± 0.182
Sodium oleate and sodium glycocholate	70	-56.30 ± 0.809	-64.60 ± 0.716	-9.61 ± 0.182
Sodium oleate and sodium glycocholate	39	-29.90 ± 0.185	-36.50 ± 0.455	-9.60 ± 0.341
Sodium linoleate and sodium glycocholate	39	-33.00 ± 0.236	-16.62 ± 0.469	-9.60 ± 0.341

* Each figure represents the average loss of weight of twenty stones shaken for one week, at 25 to 30 half revolutions per minute, at the temperature indicated.

TABLE 8—*Correlation of Relative Activity of Fatty Acids as Soaps on Basis of Their Molar Concentrations*

Fatty Acid Soap	Molecular Weight	Melting Point of Fatty Acid, C	Molar Concentration of 10% Shaking Solution	Percentage of Dissolution in 10% Solution	Ratio of Molar Concentration to Percentage of Dissolution
Sodium laurate	222.19	47.4S	0.45	100.0	222
Sodium myristate	250.22	57.5S	0.40	100.0*	250*
Sodium palmitate	278.25	63.64	0.36	62.2	172
Sodium stearate	306.23	69.70	0.32	57.6	180
Sodium oleate	304.27	14	0.32	49.0	153
Sodium linoleate	302.25	18	0.32	20.7	64

* Based on the theoretic result, as the stones were not shaken in the 10 per cent concentration. Since 71.1 per cent dissolution occurred in 5 per cent solution it is assumed that the stones would have entirely dissolved in the 10 per cent solution.

observed that the solvent capacities of the solutions were analogous to the order of activity of the fatty acids as soaps alone, but, contrary to expectations, they were not as great except in the case of sodium linoleate. This finding further supports the hypothesis that the fatty acids in bile are more concerned with maintaining the cholesterol in solution than are the bile salts, even though in normal animal bile the concentration of the fatty acids is much lower than the concentrations used in some of the shaking experiments.

In table 8 we attempted to correlate the relative activity of the various fatty acids as soaps on the basis of their molar concentrations. It will be seen, as in the case of the bile salts, that there was no correlation—indicating that the solvent activity was chiefly a chemical phenomenon. It is interesting to note that there is apparently an optimal length to the chain of carbon atoms. For example, the short chain fatty acids, such as lauric acid, are highly active as cholesterol solvents. Fatty acids with fewer carbon atoms than lauric acid, such as caprylic and butyric acid, are practically inert.

All these results indicate the importance of the fatty acids as cholesterol solvents. In other experiments we have observed that when gallstones are placed in liquid fatty acids they soon disintegrate, all the cholesterol going into solution. We believe that the solvent action of the fatty acids in bile depends on the amount of fatty acids that may be held in a watery menstruum. The fatty acids themselves are quite insoluble in water, but in alkaline solution as soaps they are decidedly more soluble. At an acid reaction the fatty acids are precipitated unless they are in a solution with a markedly reduced surface tension. In this latter function the bile salts are effective. Taurine, like all sulfonic acids, is especially effective in lowering the surface tension.

Lauric acid, of all the fatty acids, is best able to resist precipitation by electrolytes. Its ability to remain in solution in the presence of sodium chloride makes it useful as a maine soap. Sodium laurate is able to maintain a definite solution at a pH of 6 to 7. It is not surprising in the light of this, that Walsh and Ivy found lauric acid to be the most effective fatty acid in dissolving gallstones—a fact that we have completely confirmed.

The line seems clearly drawn that bile may be divided into a gallstone-forming component and a gallstone-dissolving component. These may be roughly represented by the saponifiable and the nonsaponifiable fraction in the bile. Searing and one of us (K. K. J.)¹⁸ have shown that diet has a small but definite effect in changing the ratio of saponifiable to nonsaponifiable material in the hepatic bile of the dog, an effect which is probably even greater in human beings, as suggested by our clinical studies.¹⁹ In the experiments on dogs a milk diet proved the most effective in increasing the fatty acid fraction. This is even more interesting when it is recalled that milk fat has a relatively high lauric acid content.

18 Jones, K. K., and Seering, E. A. The Saponifiable and Non-Saponifiable Matter in Bile as Affected by Diet, *Am J Physiol* **116** 87, 1936.

19 Brown and Dolkart,⁷ Mock, Brown and Dolkart.⁸

COMMENT

Efforts to correlate the type of bile acids common to a species of animals with dietary and metabolic factors have thus far been unsuccessful. Cholic acid appears to be common to all animals with the exception of guinea pigs, rabbits and certain rodents, according to Sobotka and others. Human, dog, ox, sheep and hog bile have been shown by numerous workers²⁰ to yield a mixture of cholic, desoxycholic, chenodesoxycholic and lithocholic acids on alkaline hydrolysis. Hog bile, in addition, has been shown to contain hyodesoxycholic acid.²¹ These bile acids are thought to occur in the bile in peptide-like conjugation, with aminoacetic acid and taurine as the water-soluble sodium salts.²² In man, the ox and the hog the glyco acids are more abundant, whereas in the dog the tauro acids predominate. These bile salts function chiefly in the process of digestion and absorption, where they act to maintain the water-soluble fats and cholesterol in solution or dispersion. It is still unknown whether they act in this regard as emulsifying agents only or whether they form water-soluble molecular compounds with the fats.

Wieland and Sorge²³ have reported the occurrence of a substance known as choleic acid which is water soluble and which was formerly considered a true bile acid, but which was actually found to be a coordinated compound containing one molecule of fatty acid and eight molecules of desoxycholic acid. They then suggested that the dissolving power of bile is due to the choleic acid principle. Fieser²⁴ has stated that he does not agree with this hypothesis, on the grounds that desoxycholic acid is not the most abundant of the bile acids obtained from bile and the other bile acids do not have the property of forming choleic acids. A second objection, voiced by Sekitoo,²⁵ is that desoxycholic acid does not occur free as such in bile but occurs in conjugation with aminoacetic acid and taurine, in which form it is questionable whether

20 Wieland, H, and Weyland, P. Untersuchungen über die Gallensäuren VIII. Zur Kenntnis der Lithocholsäure, *Ztschr f physiol Chem* **110** 123, 1920. Okamura, S, and Okamura, T. Ueber die Gallensäure der Kaninchengalle, *ibid* **188** 11, 1930. Windaus, A, Böhne, A, and Schwarzkopf, E. Ueber die Cheno-desoxy-cholsäure, *ibid* **140** 177, 1924.

21 Windaus, A, and Böhne, A. Ueber Hyo-glyko-desoxy-Cholsäure und über Hyo-desoxy-Cholsäure, *Ann d Chem* **433** 278, 1923.

22 Fieser, L F. *The Chemistry of Natural Products Related to Phenanthrene*, New York, Reinhold Publishing Corporation, 1936, p 123.

23 Wieland, H, and Sorge, H. Untersuchungen über die Gallensäuren II, *Ztschr f physiol Chem* **97** 1, 1916.

24 Fieser,²² p 131.

25 Sekitoo, T. Beiträge zur Kenntnis der Glykcholeinsäure aus Kaninchengalle, *Ztschr f physiol Chem* **199** 225, 1931.

the other bile acids could form compounds of stability with fatty acids which are comparable to the desoxycholic acid compounds

Veizár,²⁶ on the other hand, has shown that combinations of bile acids and fatty acids do occur in the intestinal canal. His observations have shown that combinations of desoxycholic acid and cholic acid with fatty acids are stable only in an alkaline medium down to p_H 7.1 to 7.9 and are unstable at an acid reaction of p_H 6 to 7. Combinations of sodium taurocholate and glycocholate are stable up to an acid reaction of p_H 5.9 to 6.1. He therefore has stated that he considers the taurocholates and the glycocholates of greater importance in the intestinal canal because they form water-soluble diffusible combinations which are stable in the physiologic p_H range of the intestine, which is slightly acid. While Verzar's observations on the relative importance of the various bile acids in the intestine and their activity in combinations with fatty acids do not necessarily hold for their importance in the biliary tract, they are of interest because they establish certain facts in the interrelation of the bile acids and the fatty acids.

The mechanisms whereby the cholic and other bile acids are conjugated in the animal body with taurine and aminoacetic acid are thought to be intimately associated with hepatic function. In the presence of hepatic disease, incomplete conjugation may occur, or free bile acids may be secreted.²⁷ Whipple²⁸ and Walters²⁹ have shown that small degrees of hepatic damage, subclinical as far as symptoms are concerned, result in a marked decrease in the bile salt content of the bile. Walters, Greene and Fredrickson³⁰ have reported that after relief of obstructive jaundice, a diminution in the excretion of bile salts is observed, which later returns to normal.

Andrews and his co-workers³¹ have hypothesized that gallstones form as the result of abnormalities of bile salt metabolism, occurring either primarily in the liver or as the result of an abnormal diffusion of the bile salts out of the gallbladder, allowing the cholesterol which is held in solution by the bile salts to precipitate out and form stones. They concluded that the significant factor to be considered in the forma-

26 Verzar, F, and McDougall, E. J. Absorption from the Intestine, London, Longmans, Green & Co., 1936, p. 163.

27 Sobotka, H. Physiological Chemistry of the Bile, Baltimore, Williams & Wilkins Company, 1937, p. 29.

28. Whipple, G. H. Bile Salt Metabolism, J Biol Chem **59** 623, 1924.

29 Walters, W. Obstructive Jaundice. Physiologic and Surgical Aspects, Rochester, Minn., Mayo Foundation, 1931.

30 Walters, W., Greene, C. H., and Fredrickson, C. H. Composition of Bile Following the Relief of Biliary Obstruction, Ann Surg **91** 686, 1931.

31 Andrews, E., Hrdina, L., and Dostal, L. E. Etiology of Gallstones. II. Analysis of Duct Bile from Diseased Livers, Arch Surg **25** 1081 (Dec.) 1932.

tion of gallstones is the relative ratio of the bile salts to the cholesterol content of the bile. They further stated that on the basis of their studies it seems that there is no substance other than bile salts in the bile capable of holding cholesterol in solution.³²

Reinhold, Ferguson and Hunsberger³³ have reported that in the presence of disease of the gallbladder the concentration of cholic acid was found to be significantly diminished from the normal level in bile from the gallbladder. This was attributed to increased permeability of the mucosa of the diseased gallbladder to bile salts, as suggested by Andrews and his group. These authors also expressed the opinion that in the presence of injury to the hepatic parenchyma or of obstruction of the bile ducts, alteration or suppression of the secretion of bile acid may be additional factors, on the basis of studies by Doubilet,³⁴ Riegel, Ravdin, Morrison and Potter,³⁵ McMaster, Broun and Rous,³⁶ Goff, Hrdina and Andrews,³⁷ and others.

The studies of Walsh and Ivy were the first to indicate that the role of the bile salts in maintaining cholesterol in solution is chiefly secondary to the role played by the fatty acids. Our results confirmed these findings. Using more accurate analytic methods than those employed by these investigators and making a greater number of experiments, we have obtained several interesting differences in results. Of all the various bile salt preparations used in the experiments, the sodium salt of pure cholic acid proved to have the greatest cholesterol-solvent capacity, with sodium taurocholate, sodium desoxycholate and sodium glycocholate, in the order named, next in activity. There appears to be an optimum concentration for some of the preparations used. Our results are not in agreement with those reported by Rosin³⁸ in the laboratories of

32 Andrews, E., Dostal, L. E., and Hrdina, L. Etiology of Gallstones. IV. Is Cholesterol Excreted by the Gallbladder Mucosa? *Arch Surg* **26** 382 (March) 1933.

33 Reinhold, J. G., Ferguson, L. K., and Hunsberger, A. The Composition of Human Gallbladder Bile and Its Relationship to Cholelithiasis, *J Clin Investigation* **16** 367, 1937.

34 Doubilet, H. Differential Quantitative Analysis of Bile Acids in Bile and in Duodenal Drainage, *J Biol Chem* **114** 289, 1936.

35 Riegel, C., Ravdin, I. S., Morrison, P. J., and Potter, M. J. Studies of Gallbladder Function. XI. The Composition of the Gallbladder in Pregnancy, *J A M A* **105** 1343 (Oct 26) 1935.

36 McMaster, P. O., Broun, G. O., and Rous, P. Studies on the Total Bile. III. On the Bile Changes Caused by a Pressure Obstacle to Secretion and on Hydrohepatosis, *J Exper Med* **37** 685, 1923.

37 Goff, M., Hrdina, L., and Andrews, E. Effect of Prolonged Stasis on the Bile Salt-Cholesterol Ratio, *Proc Soc Exper Biol & Med* **29**, 549, 1932.

38 Rosin, A. Ueber die Lösung von Gallensteinen, *Ztschr f physiol Chem* **124** 282, 1923.

Aschoff and Wieland She compared the dissolving effect of individual bile acids on cholesterol and pigment gallstones and found desoxycholic acid the most efficient Next in order of activity were glycocholic, cholic and taurocholic acid Her results, however, were based on an extremely small number of experiments

It is interesting to note that changes in the structure of the bile acid molecule have a marked effect on the ability of the particular acid to hold cholesterol in solution Conjugation with aminoacetic acid or taurine somewhat decreases this ability When cholic acid is oxidized to the dehydro or keto form, the solvent capacity is apparently lost Sodium dehydrocholate was practically inert in all concentrations Similarly, the oxidation of desoxycholic acid to the keto form resulted in a marked loss of solvent capacity In view of the fact that the preparation of mixed ketocholanic acid used showed moderate ability to hold cholesterol in solution, it appears that some additional substance—possibly chenodesoxycholic or lithocholic acid—is present No color reaction, however, is obtained when the Reinhold and Wilson modification of the Gregory-Pascoe method for determining cholates is used on the preparation of mixed ketocholanic acids employed in the experiments

On the basis that bile salts are of chief importance in maintaining cholesterol in solution in bile, thus preventing the formation of gallstones, much research has been carried out in an effort to bring about significant increases in the production of bile salts Sobotka³⁹ has stated the opinion that such studies are unsatisfactory at present because analytic procedures determine the concentration of only cholic acid Experimental increases or decreases in total bile acids cannot be interpreted properly, according to this author, because cholic acid may decrease in favor of desoxycholic acid, chenodesoxycholic acid, keto acids and certain abnormal forms which escape the colorimetric method used Therefore, much of the investigative work on bile salt determinations reported thus far is subject to serious question on such grounds

Our results demonstrate that bile salts are not the most essential substances for maintaining cholesterol in solution in the bile In equivalent concentrations the fatty acids were far more active as cholesterol solvents than were the bile acids The studies of the cholesterol-solvent capacity of fractions of bile showed that whether or not the animal belonged to a species which forms gallstones, if the bile was solvent for cholesterol, the solvent capacity could be isolated in the saponifiable or fatty acid fraction In addition to this fact it was observed that there was a considerable decrease in the amount of this saponifiable fraction in relation to the cholesterol content of the bile in those animals which

39 Sobotka,²⁷ p 26

form gallstones, as compared with the amount in those which never form gallstones

Whether the fatty acids as they occur in the bile function independently in maintaining the nonsaponifiable material in solution in the bile or whether they act in combination with the bile acids, as suggested by Wieland and Sorge and Verzar, cannot at present be determined. Certainly, however, more attention should be given the role of the fatty acids in the production of gallstones

SUMMARY AND CONCLUSIONS

Ketocholanic acids have a definite measurable effect in producing cholelithiasis when administered by mouth. No toxic effects were observed as far as pathologic changes in the liver or systemic manifestations following prolonged administration to dogs were concerned.

Bile from the gallbladder of the dog is so solvent for human cholesterol gallstones that we were unable to influence the rate at which human gallstones were normally dissolved in the gallbladder of the dog.

By fractionating bile of the dog and of the sheep (animals which do not form gallstones) and of the ox and of the hog (animals which do form gallstones), it was found that the solvent capacity of the bile could be isolated in the saponifiable or fatty acid fraction.

Quantitative analysis of bile from the gallbladder of these animals showed that the saponifiable fraction was relatively high in the dog and in the sheep but low in the ox and in the hog. Similar analysis of human bile showed that the concentration of the saponifiable fraction was extremely low in proportion to the nonsaponifiable or cholesterol fraction. These findings indicate that the fatty acids in the bile play an extremely significant role in maintaining cholesterol in solution and in preventing the formation of gallstones. Our studies indicate further that the action of fatty acids in this connection is much greater than the action of the bile salts or the bile acids. We do not agree that the mechanism whereby cholesterol is held in solution in the bile is chiefly a function of the bile salts.

PRIMARY CARCINOMA OF THE LUNG

A CLINICAL AND PATHOLOGIC STUDY OF ONE HUNDRED CASES

SIMON KOLETSKY, M D

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Recent reports have emphasized the high and apparently increasing incidence of primary carcinoma of the lung¹. At the Cleveland City Hospital in the eleven year period from 1927 to 1937, inclusive, there were 100 cases in which autopsy was performed, which constitute 1.3 per cent of 7,685 consecutive cases studied post mortem and 9.4 per cent of 1,064 cases of malignant tumor studied post mortem. At autopsy the lung ranked second only to the stomach as the primary site of carcinoma. While such a postmortem incidence obviously does not represent the true morbidity for the entire population, it serves to reflect again the frequency and importance of this tumor.

A summary of the salient gross and microscopic observations in these 100 cases of primary bronchiogenic carcinoma studied post mortem constitutes the substance of this paper. The attempt will be made to correlate the cell type of the tumor with the mode of growth and the dissemination, as well as with the clinical behavior and the prognosis.

HISTOLOGY

This tumor was classified on the basis of histologic character without difficulty, despite pleomorphism of varying degree. In the 100 cases there were 35 small cell carcinomas, 40 squamous cell carcinomas, 22 adenocarcinomas and 3 tumors which were classified as carcinoma simplex.

Thirty-two of the squamous cell carcinomas were either partly or well differentiated and showed keratinization and keratohyaline pearl formation. Although the pearls were inconspicuous or absent in the 8 cases in which there was poor differentiation, the diagnosis was estab-

From the Pathological Laboratory of the Cleveland City Hospital and the Institute of Pathology, Western Reserve University.

1. Weller, C. Pathology of Primary Carcinoma of the Lung, Arch Path 7 478-519 (March) 1929. Rosahn, P. D. The Incidence of Primary Carcinoma of the Lung, Am J M Sc 179 803-811 (June) 1930. Olson, K. B. Primary Carcinoma of the Lung, Am J Path 11 449-468 (May) 1935. Brines, O. A., and Kenning, J. C. Bronchiogenic Carcinoma, Am J Clin Path 7 120-133 (March) 1937.

lished by the demonstration of compact cords of large, flat, polygonal cells of squamous type with vesicular nuclei and well defined cell borders.

The diagnosis of adenocarcinoma was determined by the presence of acini lined with cuboidal or columnar cells. In 14 of the 22 cases the tumor was either partly or well differentiated and presented a fairly uniform microscopic picture. Evidence of mucinous secretion was noted in 3 of these cases. The 8 poorly differentiated adenocarcinomas exhibited a pleomorphic structure, and well formed acini could not be demonstrated in every microscopic section. In some areas the tumor cells appeared in small groups, with no differentiation, or formed atypical alveoli. Many sections showed invasion of blood vessels, with formation of tumor thrombi in the lumens.

The epithelial origin of small cell carcinoma from the mucosal lining of the bronchial tree is now generally accepted². The term small cell is preferable to the terms oat, spindle and round cell, since the latter indicate merely subvarieties based on the shape of the cell and denote no essential differences in structure. The tumor cells are small and grow in loose or compact alveolar nests which are separated by dense bands of connective tissue. Delicate collagenous bundles extend from the main framework between individual groups of cells. Nuclei are characteristically hyperchromatic and rarely reveal a nucleolus, the cytoplasm is scant and has indistinct borders. The spindle and oat cell varieties often show nuclear palisading, especially in perivascular position. Giant cells with overlapping nuclei are common. A tendency to invade the lymphatic system and the veins is characteristic and accounts for the widespread and distant metastases. Within small vessels the tumor cells frequently lose their characteristic configuration and become spherical, thus simulating white blood cells. Morphologic variations are slight. The tumor may, however, resemble a reticulum cell sarcoma closely, but special staining readily demonstrates that the round cell carcinoma produces no intercellular reticulum. Only 2 tumors were of the transitional cell type, showing compact groups of large oval cells with abundant cytoplasm, vesicular nuclei and occasional nucleoli. Both, however, showed areas of typical "small cells". That this gradation is characteristic of the small cell tumor is proved by the fact that in unquestionable cases areas of transitional cell carcinoma could be demonstrated. This suggests that the transitional cell form may represent an earlier phase in the life history of a small cell carcinoma, the later

2 Barnard, W. G. The Nature of the "Oat-Celled Sarcoma" of the Mediastinum, *J. Path. & Bact.* **29** 241-244 (July) 1926. Karsner, H. T., and Saphir, O. Small Cell Carcinomas of the Lung, *Am. J. Path.* **6** 553-562 (Sept.) 1930. Maxwell, J. Primary Malignant Intrathoracic Tumors, *J. Path. & Bact.* **33** 233-249 (April) 1930.

changes in size, shape and staining property of the tumor cells being due to degeneration or differentiation. In a number of the cases histologic comparison of postmortem material with biopsy specimens obtained at operation supported this concept in that the biopsy specimens, particularly those of distant lymph nodes, presented the microscopic picture of transitional cell carcinoma, while tumor tissue removed from the same sites at autopsy, several weeks or months later, showed typical small cell tumor.

The 3 tumors classified as carcinoma simplex did not fulfil the morphologic criteria of the small cell type, nor could they be satisfactorily classed with the squamous cell carcinomas or adenocarcinomas. The histologic picture was that of large round to polygonal cells loosely arranged in small groups with no differentiation.

GROSS MORBID ANATOMY

Small Cell Carcinoma—The distribution of the cases according to the location of the tumor in the lung, lobe or bronchus is summarized in table 1. The usual point of origin is at or proximal to the hilus of the lung. In 70 per cent of the cases the tumor involved the main stem bronchus, whereas in 70 per cent of the cases of squamous cell carcinoma the tumor originated in eparterial or hyparterial branches. The bronchus of origin usually shows slight to moderate occlusion by tumor, although diffuse mucosal involvement may occur without apparent ulceration and with no extension into the lumen. In 4 cases the process advanced along the mucosa to the trachea. The growth extends from the bronchus into surrounding tissue and forms an irregular, firm mass which compresses and infiltrates the lung or invades the mediastinum. In 9 of 21 cases of tumor arising in a main stem bronchus, the growth was essentially mediastinal, with only slight parenchymal involvement. The tumor may extend into the lung along smaller bronchi and by way of peribronchial lymphatic vessels. Pleural involvement by tumor was noted in 11 cases, in 8 of which there was bloody effusion. In 18 cases bronchial occlusion resulted in numerous small bronchiectatic abscesses, and in 3 instances there was formation of an abscess cavity, 5 cm in diameter, lined with a pyogenic membrane and showing no tumor in its wall.

In every case there was conspicuous involvement of the tracheobronchial lymph nodes by tumor, usually with almost complete obliteration of their structure (table 2). A large mass filling the superior or posterosuperior mediastinum was present in 18 of the 35 cases. The aorta and the pulmonary vessels were frequently encased in tumor. There were invasion into and thrombosis of the superior vena cava (5 cases), severe compression and displacement of the esophagus

TABLE 1—*Distribution of Carcinomas in Lung, Lobe and Bronchus*

	Number of Cases		
	Small Cell Carcinoma	Squamous Cell Carcinoma	Adeno carcinoma
Lung, 93 cases	34	37	22
Right lung	22	21	11
Left lung	12	16	11
Lobe, 85 cases	30†	36	19
Right lung			
Upper lobe	9	7	4
Middle lobe	1	2	1
Lower lobe	3	6	4
Entire lung	1	6	1
Left lung			
Upper lobe	6	10	7
Lower lobe	1	5	2
Bronchus, 84 cases	30	34	20
Right main	12	6	0
Left main	9	1	2
Eparterial	3	6	2
Hyparterial, middle lobe of right lung	1	2	1
Hyparterial, lower lobe of right lung	2	6	4
Hyparterial, upper lobe of left lung	0	5	6
Hyparterial, lower lobe of left lung	1	5	2
Branch	2	3	3

* Tumors which were described inadequately for the purpose of the table have been omitted

† Nine of the tumors were essentially mediastinal in position and showed slight or no parenchymal involvement

TABLE 2—*Tracheobronchial Lymph Nodes*

	Number of Cases		
	Total	Lymph Node Involvement	Percentage
Small cell carcinoma	33	33	100
Squamous cell carcinoma	36	24	66
Adenocarcinoma	19	16	84

TABLE 3—*Mediastinal Mass*

	Number of Cases		
	Total	Mediastinal Mass	Percentage
Small cell carcinoma	35	18	52
Squamous cell carcinoma	40	2	5
Adenocarcinoma	22	5	23

TABLE 4—*Invasion of Heart*

	Number of Cases		
	Total	Invasion of Heart	Percentage
Small cell carcinoma	35	7	20
Squamous cell carcinoma	40	4	10
Adenocarcinoma	22	4	18

(7 cases), with ulceration into the lumen in 4 instances, and lateral or anterior displacement of the trachea (6 cases). Invasion of the pericardium by direct extension occurred at its upper posterior, superior lateral and lateral aspects. Laterally, tumor extended into the pericardium from the mediastinal pleura when these became adherent as a result of infection or tumor infiltration. In 13 cases (37 per cent) there was pericardial involvement, and in 7 of these there was further extension of tumor into the wall of the auricles. In 5 cases in which clinical components of Horner's syndrome were present, tumor was seen at the thoracic inlet, and in 3 of these there was pain in the shoulder and arm due to involvement of the brachial plexus.

Squamous Cell Carcinoma—Of 37 tumors, 21 were located in the right lung and 16 in the left. The upper lobe was involved with greater frequency than the lower (table 1). The tumor usually begins distal to the bifurcation of the main stem bronchus and not proximal to it, as does the small cell type. Eparterial or hyparterial branches were the site of origin in 24 of 34 cases (70 per cent), and the right main bronchus was involved in 7 cases and branch bronchi in 3 instances. At autopsy there is a firm irregular mass at the hilus. The bronchus of origin shows considerable grayish white, crumbly tumor in its wall, with mucosal ulceration and narrowing of the lumen. The process advances along the mucosa and submucosa toward neighboring large bronchi and the main stem bronchus. Distally there is extension along smaller bronchi into the lung and frequently to the pleura, with serous or bloody effusion. Fatal hemorrhage may result from erosion of large vessels (3 cases). In 5 cases the ribs and the thoracic wall were eroded, an observation confined to the cases of squamous cell tumors. Gradual bronchial occlusion by tumor leads to peripheral bronchiectasis, with the formation of one or several abscess cavities. In 29 of the 40 cases there were small bronchiectatic abscesses (72 per cent), and in 13 cases there was a cavity, 4 cm. or more in diameter, the wall being lined with a pyogenic membrane and infiltrated by tumor. The remaining pulmonary tissue was the seat of atelectasis, chronic interstitial pneumonitis, suppuration and occasionally gangrene. Diffuse bronchiogenic spread of the tumor partly by direct aerogenous transmission led in 8 cases to consolidation of an entire lobe by grayish white soft tumor, with central liquefaction necrosis resulting in cavity formation. Thus the presence of a cavity was noted in 21 of 40 cases of squamous cell carcinoma (table 5).

The squamous cell carcinoma shows no tendency to invade the lymphatic system and metastasize to lymph nodes. However, direct extension from the bronchus of origin into adjacent bronchopulmonary lymph nodes frequently occurs, but even here the infiltration is often

slight and the nodes remain relatively intact and small. Involvement of lymph nodes beyond the hilus of the lung (i. e., tracheobronchial, at the superior or the inferior bifurcation, and paratracheal) occurred in 24 of 36 cases (66 per cent). When the tumor arose from a main stem bronchus, tracheobronchial nodes were invaded in every instance. With origin from eparterial or hyparterial branches in the upper lobe of the left lung, involvement was found in 73 per cent of cases and from hyparterial branches in the lower lobe in 54 per cent. In 2 cases a large tumor formed in the posterosuperior mediastinum (table 3). Tumor involvement of the pericardium usually occurred by direct extension from lymph nodes at the bifurcation, the pericapsular connective

TABLE 5—*Cavity Formation*

	Number of Cases		
	Total	Cavity Formation	Percentage
Small cell carcinoma	35	3	9
Squamous cell carcinoma	40	21	52
Adenocarcinoma	22	6	27

TABLE 6—*Squamous Cell Carcinoma with Tracheobronchial Lymph Node Involvement*

	Number of Cases		
	Total	Involvement of Tracheobronchial Nodes	Percentage
Main bronchus	7	7	100
Eparterial and hyparterial branches, upper lobe of left lung	11	8	73
Hyparterial branches, lower lobe	13	7	54
Branch bronchus	5	2	66

tissue of which blends with the fibrous pericardial layer in the superior mediastinum. Thus involvement was at the site of the pericardial reflection over the great vessels at the base of the heart. While such extension was present in 14 cases (32 per cent), invasion of the wall of one or both auricles occurred in only 4 cases (10 per cent).

Adenocarcinoma—The right and the left lung were involved with equal frequency, and the tumor usually began within the hilus of the lung (table 1). In 20 cases only 2 tumors involved the main stem bronchus, 3 originated in a small branch bronchus and the remaining 15 (75 per cent) involved eparterial or hyparterial branches. The bronchus of origin is occluded by tumor, and the growth extends along the mucosa toward the main stem bronchus and diffusely into the

parenchyma of the lung along small bronchi and bronchioles, the walls being replaced by carcinoma. Pleural infiltration occurred in 11 cases (50 per cent), and in 6 cases there was bloody effusion. Bronchiectatic abscesses were frequent, and in 3 cases there was an abscess cavity, 5 cm in diameter, showing tumor in its wall. Diffuse spread of the growth by an aerogenous bronchiogenic route led in 3 cases to replacement of an entire lobe by tumor, with central necrosis resulting in cavity formation (table 5). In 16 (84 per cent) of the 19 adequately described cases there was slight to conspicuous involvement of the tracheobronchial lymph nodes by tumor (table 2). Direct extension into the pericardium occurred in 8 instances (36 per cent), with invasion of the myocardium of the right or of the left auricle in 4 cases (18 per cent). Shortly before death 1 patient had auricular flutter, presumably due to involvement of the right auricle by tumor. A large tumor was present in the posterosuperior mediastinum in 5 cases (table 3). In 3 of these cases the aortic arch was partly encased in tumor which involved the recurrent laryngeal and phrenic nerves.

Carcinoma Simplex—One of the 3 tumors of this type was a circumscribed growth in the lung parenchyma. The other 2 involved hyparterial bronchi and showed extensive invasion of the lung, involvement of tracheobronchial lymph nodes and widespread metastases.

TUMORS OF THE PARENCHYMA AND BRANCH BRONCHI

In 78 of the entire group of 100 cases the tumor involved a main stem, eparterial or hyparterial bronchus. In 10 cases the tumor was not accurately located in relation to the bronchial tree, and in the remaining 12 the major bronchus was free from tumor and the growth either was in the parenchyma of the lung (4 cases) or involved a minor branch bronchus (8 cases).

The parenchymal carcinoma was a circumscribed growth, 5 to 10 cm in diameter, the origin of which could not be traced to a macroscopically visible bronchus. The mass was situated in the periphery of the lung and extended to the pleura, which in 2 instances showed irregular infiltration. Three of the tumors were squamous cell carcinomas, and 1 was carcinoma simplex. Involvement of the bronchopulmonary lymph nodes was present in 3 cases, and 2 of the tumors showed further extension to tracheobronchial nodes. In only 1 case was there extrathoracic metastasis.

In the 8 cases in which the tumor derived from a branch bronchus there was an irregularly circumscribed growth, which occasionally infiltrated the pleura. In 7 of these cases (2 small cell tumors, 2 squamous cell carcinomas and 3 adenocarcinomas) the tumor was located in the upper lobe. In all cases the regional lymph nodes were involved, and in 5 cases the tracheobronchial nodes were also involved, extrathoracic

metastases occurred in 6 cases. One squamous cell carcinoma situated in a lower lobe showed no lymph node involvement but had metastasized to the adrenal glands.

BIOPSY SPECIMENS REMOVED AT OPERATION

A summary of all the biopsies made during the clinical study of these cases is presented in table 7. These data are of importance in determining the extent and the mode of dissemination of each type of carcinoma. Almost half the specimens of small cell tumor were removed from an extrathoracic site, while the specimens of squamous cell tumor were almost uniformly obtained from within the chest and in the neighborhood of the primary tumor. Among the small cell tumors, extrathoracic superficial lymph nodes represented 45 per cent of the "positive" specimens, while, in striking contrast to this, there were no "positive" lymph node biopsy specimens of the squamous cell type. The majority of the specimens showing adenocarcinoma came from the lung, although several distant sites were represented, lymph nodes, however, were an unimportant source.

Bronchi—Fifteen (75 per cent) of the 20 specimens obtained bronchoscopically showed carcinoma. The highest percentage of positive results, as might be expected, was obtained in cases of small cell tumor, 70 per cent of these tumors involved the main stem bronchus and would have been readily visualized bronchoscopically. Of the 4 squamous cell carcinomas for which negative results were obtained on biopsy, autopsy showed that 2 originated in hyparterial bronchi of the lower lobe and 2 involved the eparterial branch at its origin without extending into the main stem bronchus.

Pleural Fluid—A dependable diagnosis of carcinoma based on microscopic examination of the pleural fluid rests on the demonstration of tissue organization of cells with a cytologic structure indicative of tumor. Diagnosis based on the cytologic structure alone or the nuclear-nucleolar ratio³ is rarely conclusive and is often hazardous. In cases of small cell tumor particularly the loss of tissue organization in a fluid medium may preclude a positive diagnosis, since the individual cells are small and may resemble blood cells and the nuclear structure may be obscured by hyperchromicity. All but one of the effusions showing carcinoma cells in the cases of squamous cell carcinoma and adenocarcinoma were hemorrhagic, and in every instance at autopsy there was tumor infiltration of the pleura. In 1 case of squamous cell carcinoma it was demonstrated that a pleural effusion showing carcinoma

³ Foot, N. C. Identification of Tumor Cells in Sediments of Serous Effusions. *Am J Path* **13** 1-12 (Jan) 1937.

cells may occur before there is any involvement of the tracheobronchial lymph nodes by tumor or any distant metastases

Lungs—Autopsy studies were made in 2 cases in which pneumonectomy had been performed for carcinoma. In each instance death occurred four weeks after the operation and was due to the development of a bronchopleural fistula with empyema. Both surgical specimens showed carcinoma involving a hyaline branch of the lower lobe. In 1 case an adenocarcinoma was revealed at autopsy at the site of excision of the hyaline bronchus, with involvement of the lymph nodes at the inferior bifurcation and with metastasis to the liver and to

TABLE 7—*Summary of Biopsy Data*

	Number of Biopsies	Positive Results
Small cell carcinoma, 35 cases (28 biopsies)		
Bronchus	8	7
Cervical node	4	4
Submaxillary node	2	2
Axillary node	3	2
Inguinal node	1	1
Pleural fluid	5	0
Lung tissue	2	2
Skin	3	2
Squamous cell carcinoma, 40 cases (34 biopsies)		
Bronchus	11	7
Intercostal nodes	2	0
Lung, aspiration (4 cases)	6	1
Pleural fluid (4 cases, positive results in 3 cases)	8	5
Lungs	2	2
Lung tissue	2	2
Sputum	1	0
Ilium (1 case)	2	1
Adenocarcinoma, 22 cases (16 biopsies)		
Bronchus	1	1
Right lung	1	1
Cervical nodes	1	1
Lung, aspiration (1 case)	2	0
Pleural fluid (4 cases, positive result in 1 case)	8	2
Skin	2	2
Sputum	1	0

the opposite lung. In the second case a squamous cell carcinoma was shown at autopsy to have been completely resected, there were no metastases.

METASTASES

The postmortem data regarding distribution of metastases are summarized in table 8. These correlate closely with the data regarding distribution of metastases obtained during life. It is again evident that the distinct difference in tendency to metastasis depends on cell type. Only 35 per cent of the squamous cell carcinomas showed extrathoracic dissemination, as compared to 89 per cent of the small cell carcinomas and 86 per cent of the adenocarcinomas.

No close parallel was found to exist between the degree of differentiation of the tumor and the extent of metastasis. The small cell carci-

nomas were undifferentiated and were not subject to grading. The poorly differentiated adenocarcinomas as a general rule showed more widespread metastases than those that were well or partly differentiated. Partly or well differentiated squamous cell carcinomas metastasized less frequently than the poorly differentiated tumors, but the extent of dissemination was approximately the same.

Small Cell Carcinomas—These are vigorously metastasizing tumors with a tendency to diffuse permeation of the lymphatic system. Groups of lymph nodes were involved by this type of tumor as follows: tracheobronchial, 100 per cent of cases; cervical, 48 per cent; abdominal, 48 per cent; axillary, 85 per cent; and inguinal, 57 per cent. The presence of carcinoma in superficial lymph nodes of the cervical, axillary

TABLE 8—*Metastases*

	Small Cell Carcinoma, Percentage	Squamous Cell Carcinoma, Percentage	Adeno- carcinoma, Percentage	Total, Percentage
Cervical nodes	48.0	0	27.0	22
Axillary nodes	85	0	0	3
Submaxillary nodes	85	0	0	3
Inguinal nodes	57	25	45	3
Abdominal nodes	48.0	12.0	27.0	27
Liver	66.0	18.0	50.0	40
Adrenal glands	54.0	12.0	64.0	38
Kidneys	20.0	15.0	36.0	21
Other lung	11.0	12.0	55.0	21
Bone	23.0	10.0	32.0	19
Pancreas	40.0	0	18.0	18
Skin	14.0	25	23.0	11
Spleen	17.0	0	23.0	11
Heart	57	25	23.0	7
Thyroid gland	85	0	45	4
Miscellaneous (number of cases)				
Small cell carcinoma	gallbladder 2, pituitary body 1, bladder 1, uterus 1, cecum 1, ileum 1, colon 1, peritoneum 1			
Adenocarcinoma	gallbladder 2, colon 2, mesentery 2, omentum 3, stomach 1, peritoneum 1, diaphragm 4			

of inguinal chains was uniformly indicative of extensive involvement of deeper groups in the thorax and abdomen. Of the organs and systems, the liver, adrenal glands and pancreas were most frequently the site of metastasis (66, 54 and 40 per cent, respectively), with the brain, skeletal system, kidneys and spleen following in that order. The skin was involved in 14 per cent of the cases. As a rule the liver was extensively replaced by tumor, the average weight of this organ in 23 cases being 2,950 Gm. The heaviest livers weighed 6,275, 6,200 and 5,200 Gm, respectively. In these cases the patient showed signs and symptoms of portal obstruction—ascites, jaundice and melena. The adrenal glands usually showed small circumscribed tumor nodules in the medulla and occasionally were almost completely obliterated by larger confluent masses. Involvement of the pancreas was more than twice as frequent in these cases as in the cases of adenocarcinoma. Solitary of

multiple nodules were present in the head, body or tail of the organ, and in 4 cases there was complete replacement of the tip of the tail by tumor

Squamous Cell Carcinomas—The squamous cell carcinomas are infiltrating, relatively nonmetastasizing tumors. In 65 per cent of the cases autopsy revealed no extrathoracic metastases, this is consistent with the fact that practically all the biopsy specimens that showed this type of tumor were obtained from the lung itself. Extensive dissemination by way of the lymphatic system does not occur, and involvement other than that of the regional lymph nodes is infrequent. The cervical and axillary chains were not involved at all, and the abdominal nodes showed invasion in 12 per cent, with 1 instance of extension to the inguinal nodes. The liver, adrenal glands and kidneys were involved in only 18, 12 and 15 per cent of the cases, respectively. There were no instances of metastases to the spleen or to the pancreas, and the heart and skin were involved only once. Metastatic tumor of the opposite lung was found in 5 cases (12 per cent). In only 6 of the 21 cases of cavity formation was there extrathoracic dissemination. Moreover, erosion of the thoracic wall and ribs by tumor occurred in 4 cases in which no metastatic lesions were observed.

Adenocarcinomas—These tumors metastasize essentially by way of the blood stream, in contrast to small cell carcinomas, which are disseminated chiefly by way of the lymphatic system. Organs, systems and regions usually invaded by a hematogenous route, such as the kidneys, adrenal glands, skeletal system, opposite lungs, skin and heart, were more frequently involved by adenocarcinoma than by the small cell tumor. Metastasis to the opposite lung occurred in 55 per cent of cases, and the skin and heart were each involved in 23 per cent of cases. As is the case with the small cell type of tumor, the cutaneous metastases are usually found in the anterior thoracic wall and the abdomen, the lesions consisting of small, round, freely movable subcutaneous nodules, occasionally attached to the corium. There was no instance of ulceration through the skin. The heart usually showed isolated circumscribed tumor nodules, 2 mm to 1 cm in diameter, situated subendocardially in the ventricular myocardium or the interventricular septum. Cardiac arrhythmia was not detected during the clinical study in these cases. The adrenal glands were the organs most frequently involved by this type of tumor (64 per cent), often extensively, with almost complete destruction. Invasion of the liver and pancreas by this type of tumor was both less frequent and less extensive than for the small cell carcinoma. The average weight of the 10 livers showing metastases was 1,780 Gm. Involvement of lymph nodes was more frequent than in the cases of squamous cell carcinoma but much less extensive and con-

spicuous than in the case of small cell carcinoma. Abdominal and cervical nodes were each invaded in 27 per cent of the cases. Extension to the inguinal nodes occurred only once, and there was no instance of involvement of the axillary or submaxillary lymph nodes.

METASTASES TO THE BRAIN

Metastatic tumor of the brain was found in 22 per cent of the entire group of cases. However, the frequency of involvement again

TABLE 9—*Metastases to the Brain*

	Number of Cases	Number of Examinations	Number of Cases of Metastasis	Percentage
Small cell carcinoma	35	12	4	33.0
Squamous cell carcinoma	40	19	1	5.3
Adenocarcinoma	22	14	5	36.0
All types	97	45	10	22.0

TABLE 10—*Clinical Data*

	Small Cell Carcinoma	Squamous Cell Carcinoma	Adeno carcinoma
Total number of cases	35	40	22
Age distribution			
30-39	5	1	3
40-49	13	11	6
50-59	13	12	7
60-69	3	11	5
70-79	1	5	0
80-89			1
Average age	46 years	56 years	51 years
Sex			
Men	33	38	16
Women	2	2	6
Race			
White	33	36	18
Negro	2	4	4
Duration of symptoms	6 months	12 months	8 months

showed a distinct difference according to the cell type (table 9). In the cases of small cell carcinoma and adenocarcinoma there were metastases in 33 and 36 per cent of the cases, respectively. These consisted of multiple round, circumscribed nodules, 0.5 to 3 cm. in diameter, in the hemispheres, basal ganglions, midbrain and cerebellum. Clinically the lesions produced weakness or paralysis of the extremities, aphasia and headaches and were mistaken for cerebrovascular accident, cerebral thrombosis or encephalomalacia. Only 1 of the 19 brains examined in cases of squamous cell carcinoma showed metastasis, a solitary tumor, 6 cm. in diameter, in the temporo-occipital lobe. In this case a clinical diagnosis of primary tumor of the brain had been made.

CLINICAL OBSERVATIONS

The distribution of the tumors according to the age, sex and race of the patients is shown in table 10. The patients with small cell carcinoma showed an average age incidence of 46 years, thus this type of tumor affects younger persons than the squamous cell carcinoma or the adenocarcinoma. The ratio of men to women in the entire series was 9 to 1, but for patients with adenocarcinoma it was only 2.7 to 1. The ratio of white to Negro patients in the 100 cases of carcinoma was 9 to 1, as compared with a ratio of 3 to 1 for all white and Negro patients who came to autopsy in the period studied.

Symptoms—Cough with or without expectoration, thoracic pain, hemoptysis and dyspnea were the most frequent symptoms in each of the three groups of cases. The complaints in the cases of squamous cell carcinoma were almost uniformly referable to the respiratory system. The chief complaints in 4 cases of adenocarcinoma were due to metastatic lesions, i. e., slow speech, vomiting, pathologic fracture of the cervical portion of the spine and pain in the back. In the cases of small cell carcinoma the frequent formation of a mediastinal tumor was responsible for a triad of symptoms—dyspnea of the obstructive type, dysphagia and dysphonia—not observed in the other cases. Dysphonia is an infrequent symptom in cases of adenocarcinoma and is rare in cases of squamous cell carcinoma. Abdominal pain and vomiting referable to metastases were occasionally prominent in the cases of small cell carcinoma. Two patients with small cell carcinoma entered the hospital complaining of a mass in the neck. The total duration of symptoms from onset to death averaged six months in the cases of small cell carcinoma, twelve months in the cases of squamous cell carcinoma and eight months in the cases of adenocarcinoma. In each of the groups medical aid was usually sought late in the course of the disease.

Tumor of the Superior Pulmonary Sulcus—No case fulfilling all the criteria for this tumor, as originally defined by Pancoast,⁴ was found in the present study. However, in 5 cases of small cell carcinoma and in 1 case of squamous cell carcinoma there were components of the "group complex" of the tumor, such as pain in the shoulder and arm, atrophy of the muscles of the hand, pupillary changes and a roentgenogram showing a shadow at the extreme apex (with local costal involvement in 1 case). In every instance these were associated with tumor at the thoracic inlet.

Clinical Diagnosis—The correct clinical diagnosis was made in 56 of the 100 cases of carcinoma. Over the entire period of eleven years

⁴ Pancoast, H. K. Superior Pulmonary Sulcus Tumor. Tumor characterized by Pain, Horner's Syndrome, Destruction of Bone, and Atrophy of Hand Muscles. *J. A. M. A.* 99:1391-1396 (Oct. 22) 1932.

the incidence of correct diagnoses was approximately the same for each of the three groups. In the last five years of the study, i. e., 1933 to 1937, inclusive, there was no essential increase in the number of cases of squamous cell carcinoma or adenocarcinoma in which a correct diagnosis was made. However, in 14 (80 per cent) of the 17 cases of small cell carcinoma for this period the correct diagnosis was made, as compared to 4 (22 per cent) of the 18 cases for the preceding six years. In the cases of squamous cell carcinoma the chief source of error was the masking of the tumor by suppurative inflammation, with a resulting picture of pulmonary abscess (6 cases). Carcinoma was mistaken for tuberculosis in 4 cases. In the cases of adenocarcinoma the incorrect final impressions were carcinoma of unknown origin with metastases (4 cases), pulmonary tuberculosis (2 cases), and carcinoma of the esophagus, encephalomalacia and pleural effusion (1 case each). In 9 cases of small cell tumor a tentative diagnosis of a malignant growth with metastases was made, but the site of origin was incorrectly ascribed, i. e., the stomach (4 cases), thyroid gland, prostate and kidney (1 case each), and mediastinum (sarcoma, 2 cases). Pulmonary tuberculosis and pulmonary abscess were each diagnosed in 3 cases of small cell carcinoma.

Preceding Pulmonary Disease—Frequently the clinical history did not give sufficient information to warrant conclusive interpretation. However, all but a few patients stated that they were in good health prior to the onset of the present illness. A past history indicating chronic pulmonary infection, such as bronchitis or bronchiectasis, was conspicuously absent. Five patients gave a history of chronic cough of one to four years' duration. Only 2 had influenza (during the epidemic of 1917), and in none of the records was there a history of previous tuberculosis. At autopsy active tuberculosis was present grossly in only 2 per cent and healed tuberculosis in 5 per cent of the cases. Pneumonoconiosis was anatomically diagnosed in 5 cases. These percentages are in accord with the postmortem incidence of tuberculosis and pneumonoconiosis in a control group of unselected cases. In the 2 cases of active tuberculosis the lesions were acute and minimal in extent and probably developed during the course of the carcinoma rather than before it.

Pulmonary Suppuration—That primary carcinoma of the lung is frequently masked by secondary pulmonary suppuration is a well known fact. This was found to be especially true of squamous cell carcinoma which is an invasive, infiltrating tumor accompanied by infection, necrosis and the formation of an abscess cavity. Not infrequently, combined clinical and roentgenographic studies do not conclusively differentiate between tumor and abscess of the lung, or they demonstrate only the

latter when both are present. Yet the diagnosis is of great importance, since surgical therapy may be indicated, especially for this type of tumor, which showed metastases in 29 per cent of cases as compared to 42 per cent for the cases of noncavitating carcinoma. Bronchoscopy is invaluable in establishing a diagnosis and should be carried out in all cases of pulmonary suppuration when the patient is over 40 years of age. Autopsy showed that this procedure would have demonstrated tumor in the 9 cases in which an erroneous diagnosis of pulmonary abscess was made.

Tumors of the Parenchyma and Branch Bronchi—Of 12 patients with tumor showing no relation to the major bronchus, 4 had no pulmonary symptoms. In 2 of these cases the tumor was incidentally observed at autopsy, in 2 others the only complaints were referable to metastatic tumor of the spine, and the primary site of the carcinoma was not discovered. The pulmonary symptoms of the remaining 8 patients, for 6 of whom a correct diagnosis was made, were few in number, consisting chiefly of cough and thoracic pain. The duration of the disease from clinical onset to death was approximately the same in this group of cases as for the cases of tumor involving the major bronchus.

COMMENT

The histologic classification of primary bronchiogenic carcinoma can be correlated with essential differences in the growth and dissemination, clinical course and prognosis in cases of each type of tumor.

The small cell carcinoma is a highly malignant tumor which metastasizes extensively and shows a tendency to widespread extension through the lymphatic system. The growth usually occurs at the hilus of the lung and infiltrates the surrounding parenchyma or grows into the posterosuperior mediastinum. Dissemination also occurs to a lesser extent by a hematogenous route. The tumor affects younger persons, and there is a rapid clinical course without notable remission. The prognosis is poor. At the onset or in the early stage of growth the tumor is surgically inaccessible. There is at present no convincing evidence of the efficacy of roentgen therapy.⁵

The squamous cell carcinoma offers the most favorable prognosis for surgical resection. The tumor is locally invasive and infiltrating and shows little tendency to metastasize. Invasion of lymph nodes occurs slowly and is usually of slight degree. In the early stage of growth the tumor may be entirely within the hilus of the lung, and complete removal can be accomplished by pneumonectomy. Autopsy studies indi-

⁵ Graham, E. A., and Singer, J. J. Successful Removal of the Entire Lung for Carcinoma of the Bronchus, *J. A. M. A.* **101** 1371-1374 (Oct 28) 1933. Edwards, A. T. Surgical Treatment of Intrathoracic New Growths, *Brit. M. J.* **1** 827-830 (May 7) 1932. Graham, E. A. Primary Carcinoma of the Lung or Bronchus, *Ann. Surg.* **103** 1-12 (Jan) 1936.

cate that with earlier clinical recognition an appreciable number of patients with this type of carcinoma could be treated surgically. One case in which complete resection was achieved, in spite of a clinical history of ten months' duration, is included in this study. The slow growth of this type of tumor, which is reflected in the comparatively long clinical course, is a distinctly favorable factor as regards prognosis. The tumor involving a hyparterial bronchus in the lower lobe appears to offer the best prognosis for complete resection, since it invades the tracheobronchial lymph nodes less frequently than do tumors in other locations (table 6).

The opportunity afforded for surgical treatment is less favorable in the case of adenocarcinoma than in the case of squamous cell carcinoma. Though the former tumor is locally invasive and infiltrating, it shows more frequent and extensive involvement of lymph nodes and metastasizes vigorously and by preference by way of the blood stream. Since the tumor occurs within the hilus of the lung, early clinical recognition renders surgical intervention feasible prior to involvement of the tracheobronchial lymph nodes or extrathoracic metastasis. Moreover, for this type of tumor, pneumonectomy may be warranted later in the course of the disease in the hope of alleviating symptoms and possibly prolonging life.

CONCLUSIONS

The histologic classification of primary carcinoma of the lung may be correlated with essential differences in the growth, dissemination and prognosis typical of each type of tumor.

The small cell carcinoma is a highly malignant tumor which offers a poor prognosis. Usually primary at the hilus of the lung, it readily invades the posterosuperior mediastinum and metastasizes extensively, with especial tendency to widespread extension through the lymphatic system. The tumor occurs in younger persons, and there is a short, rapid course without notable remission.

The squamous cell carcinoma is a slowly growing, locally invasive and relatively nonmetastasizing tumor accompanied by infection, necrosis and cavity formation. Involvement of lymph nodes other than the regional and tracheobronchial nodes is infrequent. This type of carcinoma, particularly a growth involving the hyparterial bronchus of the lower lobe, offers the most favorable prognosis for complete resection.

In cases of adenocarcinoma, surgical intervention is less favorable, since the tumor, while locally invasive, shows more frequent and more extensive lymph node involvement and metastasizes vigorously by way of the blood stream.

Dr Howard T Karsner and Dr Herbert S Reichle advised concerning this study.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JANUARY 1937
TO JUNE 1938

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A review of the literature on the gastrointestinal tract covering 1937 and the first half of 1938 must present at best a composite picture. Owing to the complicated mechanism by which the digestive tract is controlled, it is obvious that searchers after more or less isolated facts must frequently be at variance. The known variables involving the processes of digestion are becoming increasingly more numerous. Because of this fact it is more and more difficult to draw definite and lasting conclusions as to etiologic or physiologic processes.

From the anatomico-pathologic point of view little new has been added during the period covered, although there has been a constantly increasing number of observations on some of the rarer conditions. Observations based on clinical studies or animal experimentation obviously represent attempts to elucidate certain fundamentals, and discrepancies between individual investigations still serve to show how delicate and how involved is the motor and secretory function that has to do with the ingestion, preparation, absorption and elimination of food products. It is of interest that more and more scrutiny is being directed toward the relation between the central nervous system, the autonomic nervous system and the digestive tract. The importance of the psyche in its influence on digestive processes is being more clearly and logically presented. Applied pharmacology in relation to gastrointestinal physiology is increasingly productive of results, which are still, however, confused and at times discordant. Therapeutic methods are being

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revised on the basis of physiologic studies and clinical results but, as usual, leave much to be desired

The present review attempts to discuss in a more or less logical sequence what have seemed to be the most important and outstanding clinical and experimental studies

THE ESOPHAGUS

Dilatation of the esophagus has been considered from several angles Strauss,¹ in careful studies on autopsy specimens in 5 cases, noted that dilatation started above the area where the esophagus goes through the diaphragm. In younger subjects he believes that such dilatation may be due to constriction by the crura of the diaphragm, whereas in older persons he believes that most frequently it is due to relaxation of the esophageal hiatus

Etzel² presents evidence that lesions of Auerbach's plexus are not necessarily the result or the cause of esophageal dilatation. His observations were made at autopsy in 2 carefully studied cases and on sections of the esophagus of a dog with experimental constriction of that organ

McGibbon and Mather³ present data on a small group of cases in which there were areas of spasm of the esophagus at a level well above the cardia. The spasm at times gave the appearance of a so-called functional diverticulum and was transient or intermittent in some and persistent in others. It appeared to be a neurologic manifestation, at times associated with disease of other organs

An interesting study on so-called cardiospasm is that of Lendrum,⁴ based on a complete autopsy study of 150 controls, numerous animals and 13 patients with "cardiospasm." No evidence was found histologically of a true sphincter at the cardia, although there were more adventitial elastic fibers at the level of the cardia than in the middle portion of the esophagus. The myenteric plexus appeared to be the same throughout the lower two thirds of the esophagus. Histologic studies in 13 cases of "cardiospasm" showed, among other anatomic changes, a marked decrease in the number of ganglions of Auerbach's plexus in comparison with the number in control material previously studied

1 Strauss, H. Ueber hiatogene oder phrenogene Oesophagusdilatation, *Arch f. Verdauungskr* **61** 158, 1937

2 Etzel, E. La dilatación del esófago frente a las lesiones del plexo de Auerbach en el megaesófago, *Bol. y trab. de la Soc. de cir. de Buenos Aires* **21** 131, 1937

3 McGibbon, J. E. G., and Mather, J. H. Simple Non-Sphincteric Spasm of the Esophagus, *Lancet* **1** 1385, 1937

4 Lendrum, F. C. Anatomic Features of the Cardiac Orifice of the Stomach, with Special Reference to Cardiospasm, *Arch. Int. Med.* **59** 474 (March) 1937

Jonsson⁵ gives an interesting roentgenographic study of the hypopharynx and the upper portion of the esophagus in 50 normal persons, at least 18 of them showing definite bulging in the posterior wall and immediately below the cricoid cartilage, corresponding to the so-called esophageal lip of Killian. Such a finding is at times incorrectly interpreted as a sign of a foreign body. Jonsson presents in detail the anatomic relations at the esophageal mouth and discusses the correspondence between the so-called esophageal lip and a pulsion diverticulum.

Of moderate interest is the report of Wallace,⁶ who reviewed the histories of 26 patients for whom a roentgen diagnosis of traction diverticulum of the esophagus had been made. Contrary to the usual conception that such diverticula are most frequently asymptomatic, over one third of Wallace's patients presented symptoms, varying from acute hematemesis to substernal pain and dysphagia.

Benedict and Daland⁷ present the curious complication of benign stricture of the esophagus and duodenal ulcer, with a discussion of previously reported cases.

Of slight interest is the report by Piquet and Tison⁸ on the apparent relation between alcoholic addiction and cancer of the esophagus. Of 110 patients with cancer of the esophagus, 102 were exceedingly heavy drinkers.

The surgical treatment of cancer of the esophagus still presents almost insuperable technical difficulties. Several successful operations on individual patients have been noted, however, and Garlock⁹ reports in detail on 3 patients who were successfully operated on for lesions of the thoracic portion of the esophagus. The technic and the preoperative and postoperative care are described in great detail.

THE STOMACH

Numerous studies have been carried out regarding the relation between the central nervous system and the control of gastric secretion. Heslop,¹⁰ in a carefully performed set of experiments on cats and dogs,

5 Jonsson, G. Notes on the X-Ray Picture of the So-Called Esophagus Lip, *Acta radiol.* **18** 452, 1937.

6 Wallace, R. P. Traction Diverticulum of the Esophagus, *Arch. Int. Med.* **60** 454 (Sept.) 1937.

7 Benedict, E. B., and Daland, E. M. Benign Stricture of the Esophagus Complicating Duodenal Ulcer, *New England J. Med.* **218** 599, 1938.

8 Piquet, J., and Tison. Alcool et cancer de l'oesophage, *Bronchoscop., œsophagoscop. et gastroscop.*, April 1937, p. 137.

9 Garlock, J. H. Operation Cancer of the Esophagus, *Surg. Gynec. & Obst.* **66** 535, 1938.

10 Heslop, T. S. The Nervous Control of Gastric Secretion. An Experimental Study, *Brit. J. Surg.* **25** 884, 1938.

for the most part confirmed previous experimental work on this subject. He concludes from his observations that the response of gastric secretion to histamine is independent of nervous influences. Pure acid juice was obtained after stimulation with histamine, despite section of the fibers of the splanchnic and vagus nerves. He thinks that the secretion of mucus by the stomach is partly under the control of the sympathetic portion of the autonomic nervous system and that the splanchnic nerves contain parasympathetic as well as sympathetic fibers. Localized stimulation of the anterior and posterior portions of the hypothalamus produced parasympathetic and sympathetic effects.

Various investigators have elaborated on Cushing's earlier suggestions on the relation between a lesion of the midbrain and concurrent ulceration of the stomach or duodenum. Koga¹¹ reports experiments on rabbits with injury to the region of the third ventricle. In one third of the experimental animals there were hemorrhages and erosions in the gastric mucous membrane, while there were none in the control animals. Fifty per cent of 18 animals after resection of the vagus nerve below the diaphragm showed similar lesions, while 60 per cent of 32 animals after resection of the splanchnic nerve and the solar and superior mesenteric ganglions showed gastric lesions. It was thought that the lesions were due to local secretory disturbances and that they were different from the usual peptic ulcer.

The experimental lesions of the central nervous system produced by Chiariello¹² were fundamentally in accord with those just noted. Lesions involving the optic thalamus in dogs, along with other nuclei to some extent, were associated with hemorrhagic changes in the gastric mucosa. The author believes that these vascular lesions are fundamental and that they are characteristic of severe lesions of the midbrain but have nothing in common with true peptic ulcer. They show, he thinks, only that certain points of the nervous system, especially of the optic thalamus, are true trophic centers for the mucosa of the digestive tube.

Martin and Schnedorf,¹³ in a study on monkeys and cats, produced small isolated lesions by electrocoagulation in the hypothalamic area. Unlike the findings in the previous studies, in which the trauma to the brain tissue was undoubtedly much more extensive, all the autopsy observations, as well as studies of the stools and vomitus, failed to

11 Koga, H. Tierexperimentelle Untersuchung über die Magenveränderung bei der Läsion des Vorderhirns und des autonomen Nervensystems, *Arch f klin Chir* **188** 449, 1937.

12 Chiariello, A. G. Lesioni sperimentali del sistema nervoso centrale ed ulcera gastrica, *Rassegna internaz di clin e terap* **18** 489, 1937.

13 Martin, J., and Schnedorf, J. G. The Absence of Changes in Gastric Activity and of Gastro-Intestinal Ulceration Following Hypothalamic Lesions in the Monkey and Cat, *Am J Physiol* **122** 81, 1938.

show any evidence of gastric ulceration. There were also no changes in gastric secretion.

The case presented by Vanzant¹⁴ of a duodenal ulcer with melena, apparently occurring twenty days after an acute injury of the brain, is of interest in relation to Cushing's cases and to the aforementioned experimental work.

Vascular gastric lesions, similar to those just referred to, were procured by Dodds¹⁵ in rabbits after the subcutaneous injection of an extract of the posterior lobe of the pituitary body. If the gastric contents were neutralized by the administration of alkali previous to the administration of the extract, no lesions were produced. Extract of the anterior lobe appeared to have no effect. Extract of the posterior lobe, however, when given by mouth, apparently had a direct local effect in producing ulceration. Dodds believes that his findings confirm the idea that the secretion of the posterior lobe of the pituitary body is essential to normal gastric secretion but that at present it is impossible to apply these experiments clinically.

By inference, Snapper's¹⁶ report on 5 patients with insufficiency of the anterior lobe of the pituitary body and associated complete gastric achylia is of interest, suggesting as it does a possible physiologic effect of the anterior lobe on gastric secretion.

That gastric secretion is only in part mediated by the vagus nerves is verified by the observations of Nicolini,¹⁷ who performed numerous gastric analyses on a group of patients with postencephalitic Parkinson's disease who were receiving atropine therapy. In spite of evidences of paralysis of the vagus nerve after use of the drug, it was not possible consistently to reduce the gastric acidity. As in previous investigations, varying effects of the drug on gastric secretion were noted, but the writer stresses particularly that gastric secretion apparently can be entirely independent of vagal activity.

Gastric secretory studies after standardized surgical procedures, while inconclusive, are still of some interest. Holman and Sandusky¹⁸ completely review the literature on gastric acidity after gastroenterostomy and point out the wide variation in the results which have been reported.

14 Vanzant, F. R., and Brown, J. A. A Case of Peptic Ulcer in a Child Following Brain Injury, *Am J Digest Dis & Nutrition* **5** 113, 1938.

15 Dodds, E. C. *Recherches récentes sur le lobe postérieur de l'hypophyse*, *Paris med* **2** 274, 1937.

16 Snapper, I. Relation Between Anterior Pituitary Insufficiency and Function of Stomach and Bone Marrow, *Nederl tijdschr v geneesk* **81** 265, 1937.

17 Nicolini, E. La funzione secretoria dello stomaco in rapporto alla somministrazione cronica di forti dosi di belladonna (ricerche su encefalitici in cura bulgara), *Studium* **28** 97, 1938.

18 Holman, C., and Sandusky, W. R. Gastric Acidity After Gastro-Enterostomy, *Am J M Sc* **195** 220, 1938.

They call attention to the pitfalls of secretory studies after the Ewald test meal. By using a more careful technic, consisting of the constant suction method of Bloomfield and Pollard and stimulation with histamine, they found that the actual acidity of the gastric secretion was not materially altered by posterior gastroenterostomy in 92 per cent of 75 patients investigated. This appeared to be true in practically all cases, regardless of the duration of time after operation. The authors conclude that the titratable acidity determined before and after operation cannot be used as a prognostic criterion of the therapeutic results of gastroenterostomy.

Strauss and Necheles and their associates,¹⁹ after detailed studies made on 44 patients who had been subjected to subtotal gastrectomy for ulcer, conclude that there is no real correlation between clinical results and certain physiologic variables, such as the emptying time of the stomach, the hunger motility of the stomach, the gastroscopic appearance of the stomach, gastric analysis, preoperative anemia and clinical symptoms. The only constant finding, according to these investigators, is the correlation between the postoperative results and the gain in or loss of weight. Somewhat similar conclusions were arrived at by Gorvett and Talbot.²⁰ In 26 carefully studied cases these investigators were unable to find any correlation between the preoperative gastric acidity and the postoperative level, although in 65 per cent of the cases the Ewald meal showed postoperative achlorhydria. No constant changes in the blood were noted postoperatively. The emptying time of the stomach after operation in four fifths of the cases was less than three and one-half hours (at the lower limit of normal), but one fifth of the patients still had a normal emptying time. There was no evidence of gastric dilatation in any of the cases. Eighty per cent of the patients maintained their weight or gained weight after operation. The patients were studied at periods of from five months to two years after operation.

Two rather interesting observations on gastric secretion are presented by Schiff²¹ and by Brown and Dolkart.²² Schiff carried out nearly 80 separate gastric analyses for a single patient over a period of four and one-half years. Gastric secretion was stimulated by the use of histamine. There was a definite variation in the level of gastric

19 Strauss, A. A., Strauss, S., Levitsky, P., Scheman, L., Lerdmon, E. E., Arens, R. A., Meyer, J., and Necheles, H. Physiological and Clinical Study of Patients After Subtotal Gastrectomy, *Am J Digest Dis & Nutrition* **4** 32, 1937.

20 Gorvett, E. A., and Talbot, E. S. Physiologic and Symptomatic Expectancy Following Subtotal Gastrectomy, *Am J M Sc* **193** 345, 1937.

21 Schiff, L. Gastric Secretion in Man. Observations on the Effects of Repeated Injections of Histamine and on Transient Achlorhydria, *Arch Int Med* **61** 774 (May) 1938.

22 Brown, C. F. G., and Dolkart, R. E. Gastric Acid During Recurrences and Remissions of Duodenal Ulcer, *Arch Int Med* **60** 680 (Oct) 1937.

acidity over this period, and it is interesting to note that temporary periods of relative achlorhydria were observed. There was no evidence that repeated stimulation with histamine caused fatigue of the secretory apparatus, and with the dosage used, there was no evidence of abnormal gastric symptoms. It is also interesting to note that the intrinsic anti-anemic factor was present in all the samples obtained, including those taken during periods of achlorhydria. Brown and Dolkart made observations on 20 patients and 5 controls, the average period of observation being a little over three years. An average of 50 gastric analyses were made for each patient with the Ewald meal. Fifteen of the patients had duodenal ulcers, which had been present for an average of eleven years. Careful observations regarding seasonal incidence and recurrences of the ulcer seemed to indicate that although gastric acidity varied widely, there was no relation between the level of acidity and the degree of symptoms present or any other evidence of ulcer activity. A second group of patients with ulcer failed to show any significant reduction of acidity during fasting while under strict treatment of the Sippy type or otherwise. These studies are chiefly important because of the long period of observation and because of the demonstration of wide fluctuations of gastric secretion in normal and diseased patients.

Another set of clinical observations on gastric secretion is that of Comfort, Butsch and Eusterman,²³ who examined the gastric secretory activity of 79 patients in whom cancer of the stomach developed after the first gastric analysis. The average length of time intervening between the first gastric analysis and the subsequent diagnosis of cancer of the stomach was six years. Twenty-eight of the patients retained free acid at a practically unchanged level even after the development of cancer. Achlorhydria developed during the six years in those patients particularly who originally had low values for acid. Although these studies are of some interest, they give little further information as to the histologic relation between achlorhydria and cancer of the stomach. They suggest, however, that a diminution in the secretory activity of the stomach *per se* has no causative relation to the development of cancer.

An added item of some interest is the finding of Fabian²⁴ that the amount of salivary secretion is reduced in gastric cancer, achylia gastrica and pernicious anemia but particularly in pernicious anemia. This diminution is essentially one of quantity, as the chloride content of the saliva is only slightly diminished and the ferment content not at all.

23 Comfort, M. W., Butsch, W. L., and Eusterman, G. B. Observations on Gastric Acidity Before and After the Development of Carcinoma of Stomach, *Am J Digest Dis & Nutrition* 4 673, 1937.

24 Fabian, G. Untersuchungen über die Speichelsekretion bei Magencarcinom, perniziöser Anämie und Achylia gastrica, *Ztschr f klin Med* 131 403, 1937.

Studies of gastric motility continue to indicate the existence of various factors influencing this function. Andersen²⁵ demonstrated by means of an intragastric balloon attached to a kymograph that the administration of food through a duodenal tube was associated with absolute lack of gastric constriction provided the stomach was emptied. The presence of a little food in the stomach appeared to initiate gastric motor activity, which was already slightly modified by duodenal feeding. The results of these experiments are mainly confirmatory of the already known value of duodenal feedings in intragastric disease.

The effect of bilateral resection of the splanchnic nerves on gastric motility was studied by Barron and Curtis²⁶ in 2 cases. Observations on the gastric motor mechanism were made before operation. Subsequent to unilateral resection of the splanchnic nerves there was no change in the average rate of gastric emptying, but after bilateral resection there was a decrease of well over an hour in the emptying time, with a definite increase in the number and in the amplitude of the contractions and a marked increase in the duration of periods of gastric motility. These findings were noted for at least seven months.

Sleeth and Van Liere²⁷ demonstrated in dogs that a low environmental temperature decreased the emptying time of the stomach, whereas an elevation of the temperature surrounding the body increased it. At 15 F the gastric emptying time was 17 per cent less than normal, and at 90 F it was increased 10 per cent. The same investigators²⁸ also found that the administration of digitalis definitely decreased the emptying time of the stomach in healthy young men. The administration of 5 cc of tincture of digitalis mixed with a standard test meal reduced the gastric emptying time from 13 to 25 per cent. Clinical confirmation of these studies is apparently afforded by Hollander's²⁹ observations on 5 patients with so-called pylorospasm. After the administration of two thirds of a digitalizing dose by Eggleston's method, the administration of tincture of digitalis produced definite relief in all 5 patients when added to a regime that had previously been unsuccessful in controlling their symptoms.

25 Andersen, M. Gastrographic Studies Under Administration of Food Through Duodenal Tube, *Acta med Scandinav* **93** 437, 1937.

26 Barron, L. E., and Curtis, G. M. Late Effects of Bilateral Resection of Splanchnic Nerves on Human Gastric Motor Mechanisms, *Am J Physiol* **120** 356, 1937.

27 Sleeth, C. K., and Van Liere, E. J. Effect of Environmental Temperature on Emptying Time of Stomach, *Am J Physiol* **118** 272, 1937.

28 Van Liere, E. J., and Sleeth, C. K. Immediate Effect of Tincture of Digitalis on the Emptying Time of the Human Stomach, *Arch Int Med* **61** 83 (Jan) 1938.

29 Hollander, E. Treatment of Pylorospasm with Digitalis. Report of Five Cases, *Am J Digest Dis & Nutrition* **4** 158, 1937.

Studies on the hunger mechanism were carried out by Manville and Munroe,³⁰ who performed ileogastrostomy on dogs and observed motor and secretory activity after the administration of 10, 20 or 25 per cent solution of dextrose intragastrically. They found, as have previous observers, that hunger contractions were inhibited by the introduction of dextrose solution into the stomach. The reappearance of gastric motility was not always associated with a drop in the blood sugar content. Dextrose solution so introduced was also found to inhibit gastric motor activity induced with pilocarpine hydrochloride and insulin, and a similar inhibitory effect was obtained on gastric secretion provoked with histamine, pilocarpine hydrochloride, insulin and sham feedings. The investigators feel that there was genuine dissociation between secretory and motor activity.

Lalich, Youmans and Meek³¹ studied in dogs the effect of insulin on gastric motility. The injection of insulin into intact dogs has previously shown an augmentation of gastric motility, but after vagotomy the stimulation is replaced by inhibition, even though the gastric musculature may recover some of its tonus. This inhibitory effect of insulin on gastric motility after vagotomy persisted after section of the splanchnic nerves, after removal of the celiac ganglions and after removal of one adrenal gland and the medullary portion of the other. The authors believe that they have obtained evidence that the normal stimulating effect of insulin on gastric motility is through the vagal centers and that the inhibition of gastric motility becomes apparent only with elimination of abdominal vagal stimulation.

An interesting set of experiments on the factor of muscle spasm in the etiology of jejunal ulcer was carried out by Fauley and Ivy.³² These were similar to previous experiments performed on dogs by Steinberg and Starr. The latter investigators concluded from their experiments that muscle spasm is essential to the formation of jejunal ulcer. The procedure consisted in performing gastrojejunostomy and at the same time denudation of the muscular layers of the jejunum adjacent to the anastomosis after the duodenal contents had been diverted into the terminal portion of the ileum. In the original experiments, ulcer did not develop in the denuded area. The experiments conducted by Fauley and Ivy were identical except that the anastomosis was end to end instead of side to side. Of 14 dogs successfully operated on, 13 died of ulcer at the usual site in from ten to twenty-three weeks.

30 Manville, I. A., and Munroe, W. R. Studies on the Gastric Hunger Mechanism. II. The Inhibitory Effect of Dextrose Solutions, *Am J Digest Dis & Nutrition* **4** 561, 1937.

31 Lalich, J., Youmans, W. B., and Meek, W. J. Insulin and Gastric Motility, *Am J Physiol* **120** 554, 1937.

32 Fauley, G. B., and Ivy, A. C. The Factor of Spasm in the Etiology of Jejunal Ulcer, *Am J Digest Dis & Nutrition* **4** 160, 1937.

and the findings led to the conclusion that local muscular spasm is not essential to the development of jejunal ulcer after gastrojejunostomy

The effect of various drugs on gastric secretion has been a source of study for several years. In a carefully prepared paper Babkin³³ discusses in detail the physiologic action of histamine. There is extensive reference to the literature but no detailed description of his own unpublished experimental work. He aims to show that in the normal processes of gastric secretion during which histamine is liberated or as a result of the subcutaneous administration of histamine, of electric stimulation of the vagus nerves or of sham feedings in dogs with esophagotomy, there is an inherent possibility of pathologic disturbances which may eventually lead to damage of the gastric or duodenal wall so as to result in peptic ulcer. The suggestions contained in this work are stimulating although not new. The article presents a fairly comprehensive résumé of this conception of gastric secretory activity. The author says that Necheles' theory of ulcer formation due to the output of acetylcholine is "tempting" but finds inconsistencies in it.

Rivers and Vanzant,³⁴ using a double histamine test, i. e., a second injection of histamine one hour after the original administration of the drug, found nearly an equal increase in the amount of gastric pepsin after each injection of histamine. They conclude that histamine not only washed out the preformed pepsin but also stimulated increased production of the ferment.

Necheles,³⁵ following the knowledge that parasympathetic stimulation liberates acetylcholine and that stimulation of the gastric division of the vagus nerve causes acetylcholine to appear in the venous blood from the stomach, attempted a new approach to the genesis of peptic ulcer. Perfusion experiments in rats and dogs show that acetylcholine tends to produce anoxemia of the gastric tissues, which theoretically would be more marked over those areas most richly supplied with vagus fibers. He postulates the hypothesis that ulcer may frequently be due to an overproduction of acetylcholine in such areas in patients who are subject to excessive autonomic stimulation.

Experiments by Necheles, Motel, Kosse and Neuwelt³⁶ on the action of acetylbetamethylcholine and prostigmin on gastric secretion in

33 Babkin, B. P. The Abnormal Functioning of the Gastric Secretory Mechanism as a Possible Factor in the Pathogenesis of Peptic Ulcer, *Canad. M. A. J.* **38** 421, 1938.

34 Rivers, A. B., and Vanzant, F. R. A Study of Peptic Activity by Means of the Double Histamine Test, *Am. J. Digest. Dis. & Nutrition* **4** 304, 1937.

35 Necheles, H. A Theory on the Formation of Peptic Ulcer, *Am. J. Digest. Dis. & Nutrition* **4** 643, 1937.

36 Necheles, H., Motel, W. G., Kosse, J., and Neuwelt, F. The Effect of Acetyl-Beta-Methyl-Choline and Prostigmine on the Secretion of the Stomach of Man and Dog, *Am. J. Digest. Dis. & Nutrition* **5** 224, 1938.

man and dog attempted to further the aforementioned hypothesis. These workers showed in dogs with a Heidenhain pouch an increase in gastric acidity, in volume of gastric secretion and in pepsin secretion after injections of acetylbetamethylcholine. They found that this drug and histamine were synergistic in relation to gastric secretion. The drug stimulated gastric secretion in human beings, provided care was taken to avoid the swallowing of saliva. Saliva was found to inhibit the secretion of gastric acid induced by the drug. Somewhat similar results were obtained with prostigmin, and the authors take care to advise against the use of either of these two drugs in the treatment of peptic ulcer, as proposed in the literature. The experiments of Banting³⁷ on overstimulation of the parasympathetic nervous system by acetylbetamethylcholine in animals seems to confirm Necheles' view. Banting found lesions typical of peptic ulcer in the stomach of his animals, in addition to a certain number of colonic lesions.

The effect of aluminum preparations on gastric acidity and secretory activity was studied by Ivy and his associates³⁸. They found in 6 graduate students who were accustomed to using the stomach tube that the administration of aluminum preparations reduced free acidity for forty-five minutes or longer. There was a variation in individual subjects, and a definite tendency to an increase in acidity after aluminum had been evacuated was characteristic of 4 of the subjects.

Beazell, Schmidt and Ivy³⁹ also carried out observations on the effect of aluminum hydroxide on absorption from the gastrointestinal tract. By *in vitro* experiments it was shown that the activity of pancreatin was unaltered by the presence of aluminum hydroxide. In 3 dogs, liberal amounts of aluminum hydroxide cream, when added to a day's ration, increased the total bulk of the stools but produced no increase in the nitrogen or fat content.

Culmer, Atkinson and Ivy⁴⁰ demonstrated that solution of hydrogen peroxide acts as a definite depressant of gastric acidity. There appears to be wide individual variation. Apparently the stronger the solution of hydrogen peroxide, the greater the depression of gastric acidity. The authors believe, however, that the drug is not a satisfactory clinical

37 Banting, F. G., and Hall, G. E. The Experimental Production of Myocardial and Coronary Artery Lesions, *Tr. A. Am. Physicians* **52** 204, 1937.

38 Ivy, A. C., Terry, L., Fauley, G. B., and Bradley, W. B. Effect of Administration of Aluminum Preparations on Secretory Activity in Gastric Acidity of Normal Stomach, *Am. J. Digest. Dis. & Nutrition* **3** 879, 1937.

39 Beazell, J. M., Schmidt, C. R., and Ivy, A. C. The Effect of Aluminum Hydroxide Cream on Absorption from the Gastrointestinal Tract, *Am. J. Digest. Dis. & Nutrition* **5** 164, 1938.

40 Culmer, C. U., Atkinson, A. J., and Ivy, A. C. Hydrogen Peroxide as a Depressant of Gastric Acidity, *Am. J. Digest. Dis. & Nutrition* **4** 219, 1937.

preparation and point out that its use in the treatment of ulcer is associated with the danger of precipitating an acute hemorrhage. These findings are of interest in view of the use of solution of hydrogen peroxide in the treatment of gastritis, wherein only beneficial results have been claimed for it.

Studies on the cephalic (psychic) phase of gastric secretion have been carried on by Wilhelmj, McCarthy and Hill⁴¹. In a brief study it has been shown that the presence of tenth-normal hydrochloric acid in the stomach and in the upper portion of the intestine causes definite inhibition of the intragastric chemical and intestinal phases of acid secretion. In most instances these authors are able to show that the psychic phase of acid secretion can break through the inhibitory effect produced by the presence of acid in the stomach and duodenum and can cause a fairly high rate of acid secretion. The secretory energy of the psychic phase of gastric secretion may often exceed that due to the intragastric or intestinal phases, and it is believed that it is possible for the psychic phase of secretion to be responsible for a degree of hyperacidity unattainable by the other two phases alone.

Some scattered observations related to gastric physiology are of interest.

The bactericidal power of gastric juice, which has long been recognized, has been studied by Sebastianelli⁴². Studies carried out on a large number of specimens of gastric juice appeared to show that the bactericidal power of whole gastric juice on colon bacilli is much greater than that due to gastric acidity alone. Gastric juice which is intensely acid possesses little, if any, greater bactericidal power than gastric juice of low acidity.

Thiele⁴³ records that values for the calcium content of the blood run parallel with the titratable gastric acidity. The calcium content is especially low in cases of gastric carcinoma, and the intravenous administration of calcium appears to increase the gastric acidity.

Christiansen⁴⁴ has continued to make observations on azotemia, which is often associated with fever in gastrointestinal hemorrhage. This may be present in the absence of vomiting or associated renal disease. The striking increase in the urea content of the blood after massive intraintestinal hemorrhage is discussed, and various possible

41 Wilhelmj, C. M., McCarthy, H. H., and Hill, F. C. Acid Inhibition and Cephalic (Psychic) Phase of Gastric Secretion, *Am J Physiol* **120** 619, 1937.

42 Sebastianelli, A. Sul potere battericida del succo gastrico. Rapporti fra acidità e potere battericida del succo gastrico, *Polislinico (sez. prat.)* **44** 1593, 1937.

43 Thiele, W. Magenacidität und Kalkstoffwechsel, *Klin. Wchnschr.* **16**: 165, 1937.

44 Christiansen, T. Biochemical Changes in the Organism Produced by Massive Intraintestinal Hemorrhage, *Rev. Gastroenterol.* **4** 166, 1937.

explanations are offered for its occurrence. None of these explanations seems adequate either to the author or to the reviewers, but the chemical finding is of interest.

Another isolated finding involving the chemical analysis of the blood is that of Offenkrantz and Feraro,⁴⁵ who studied the cholesterol content of the serum of patients with peptic ulcer. The total cholesterol value was significantly lower than normal figures. This reduction appeared to be due to a fall in the value for cholesterol esters. The authors attempt no explanation but feel that the finding is of some interest and significance in view of the fact that most of the patients were being treated with the high fat diet common to most ulcer regimens.

Although of little practical value, the study of the diastase content of the blood of patients with ulcer by Probst, Gray and Wheeler⁴⁶ is of some clinical interest. Diastase determinations were obtained for 9 patients who came to autopsy as a result of an acute perforated ulcer. In the 3 cases in which the ulcer involved the pancreas, the diastase content was found to be moderately elevated above normal. In 1 instance it was at an exceedingly high level and was well within the range of values found in acute pancreatitis. In the 5 cases in which the pancreas was not involved, the values obtained were all normal. The authors conclude that a normal or low diastase value not only rules out acute pancreatitis, as is generally accepted, but also rules out penetration of a peptic ulcer into the pancreas.

Hollander⁴⁷ suggests a modification of the Bloomfield-Kerfer technique of gastric analysis. He observes that the use of phenolphthalein as a dilution indicator in gastric analysis is unsatisfactory because of loss by precipitation at a high p_H , he suggests the substitution of phenol-sulfonphthalein (phenol red).

Woldman⁴⁸ suggests a new simple test for the determination of a break in the continuity of the mucous membrane of the gastrointestinal tract. The test is based on the fact that phenolphthalein given by mouth is excreted almost in toto in the feces. Unless large amounts are taken, that appearing in the urine is in the conjugated form and does not give an immediate color reaction with sodium hydroxide. The test consists of the introduction of 1 per cent alcoholic solution

45 Offenkrantz, F. M., and Feraro, F. A Study of Serum Cholesterol in Patients with Peptic Ulcer, *J. Lab. & Clin. Med.* **22**: 780, 1937.

46 Probst, J. G., Gray, S. H., and Wheeler, P. A. Blood Diastase in Acutely Perforating Peptic Ulcer, *Proc. Soc. Exper. Biol. & Med.* **37**: 613, 1938.

47 Hollander, F., Penner, A., and Saltzman, M. Determination of Phenol Red in Gastric Contents, *Proc. Soc. Exper. Biol. & Med.* **36**: 568, 1937.

48 Woldman, E. E. A Simple Test for Determining the Presence of Gastrointestinal Lesions, *Am. J. Digest. Dis. & Nutrition* **5**: 221, 1938.

of phenolphthalein by mouth during fasting and the testing of the urine at two and four hour intervals. If phenolphthalein appears in the urine, this is interpreted as evidence that there is a break in the gastrointestinal mucous membrane. For 212 patients and normal persons the test is said to have been correct, with an error of less than 3 per cent.

Crohn and Schwartzman⁴⁹ present an interesting and probably important paper on recurrences of ulcer in association with infection of the upper respiratory tract. The clinical fact appears to be well established and is familiar to most clinicians. The authors propose that the Schwartzman phenomenon is operative in such recurrences and believe that a state of reactivity is set up in patients with ulcer by secondary bactericidal invaders. Once this state is set up, local infection may be produced by viruses or by bacteria which produce infection in the intestinal organs. Several examples of recurrences of ulcer, especially with hemorrhage, are presented in association with intercurrent infection of the respiratory tract.

The experimental production of peptic ulcer continues to interest numerous investigators. In an earlier portion of this review, allusion was made to various theories of ulcer formation, either by abnormal stimulation of the autonomic nervous system or by the local action of acetylcholine, histamine or other substances. Of the various methods for the experimental production of ulcer that have been recently reported, the following are chosen, not as providing absolutely new material but as exemplifying stimulating investigative work.

Stalker, Bollman and Mann⁵⁰ carried out numerous observations on experimental ulcers due to cinchophen. They previously described this method in the production of peptic ulcer in dogs, after the original findings of Churchill and Van Wagoner. In the present studies the authors confirmed the results of their previous investigations, in 77 dogs given cinchophen they found an incidence of 96 per cent of ulcer formation. The larger the dose, the more rapid the formation of the ulcer. For the most part, the ulcer was found on the lesser curvature of the stomach, although a few duodenal ulcers were noted. The use of bone in the diet seemed to extend ulcer formation but did not delay

49 Crohn, B. B., and Schwartzman, G. Ulcer Recurrences Attributed to Upper Respiratory Tract Infection, *Am J Digest Dis & Nutrition* **4** 705, 1938.

50 Stalker, L. K., Bollman, J. L., and Mann, F. C. Prophylactic Treatment of Peptic Ulcers Produced Experimentally by Cinchophen, *Am J Digest Dis & Nutrition* **3** 822, 1937, Effect of Cinchophen on Gastric Secretion. Experimental Study, *Arch Surg* **34** 1172 (June) 1937, Experimental Peptic Ulcer Produced by Cinchophen, *ibid* **35** 290 (Aug) 1937. Bollman, J. L., Stalker, L. K., and Mann, F. C. Experimental Peptic Ulcer Produced by Cinchophen, *Arch Int Med* **61** 119 (Jan) 1938.

healing after the use of cinchophen. Regardless of the method of administration, cinchophen produced ulcers. A characteristic of the cinchophen ulcer is that it starts with destruction of the mucosa and progresses as does peptic ulcer in man. From observations made on animals on which various agents were employed that are used in the treatment of ulcer in human beings, the authors conclude that gastric acidity is an important factor in the production of a cinchophen ulcer. The taking of alkaline powders or milk or gastroenterostomy preceding the administration of cinchophen prevented the formation of an ulcer. Other measures were less efficacious. Exclusion of the pylorus prior to the administration of cinchophen prevented the formation of an ulcer in the excluded portions. Studies of gastric secretion led to the conclusion that the administration of cinchophen resulted in no change in the level of acidity. There appeared to be hypersecretion when the ulcer had fully developed, followed by hyposecretion with omission of the drug. The ulcer produced was usually single and was found on the lesser curvature of the stomach. It appeared to be preceded by acute gastritis, which was less severe after the first two weeks. An ulcer of the perforating type developed in three weeks and gave the appearance of being chronic.

Simonds,⁵¹ in a histologic study of the material originally described by Van Wagoner and Churchill, summarizes his conclusions as follows: "The feeding of old cinchophen to dogs is the most effective method of producing peptic ulcers, resembling in all essentials the spontaneous ulcer in man." Histologically the sequence of events is that of severe gastritis, which may be diffuse and mild and is accompanied by plasma cell infiltration of the mucosa, or it may be focal and may be characterized by the formation of small abscesses in any level of the mucosa. This gastritis occurs apparently within twenty-four hours after the initial feeding of cinchophen and therefore precedes the ulcer. It is believed to be an important factor in its causation.

The principle of the production of ulcer by the exclusion of bile from the small bowel is not new. Various methods have been tested, but the study of DeBakey⁵² on the relative productive value of these is noteworthy in that it reveals the conflicting interests in the experimental production of ulcer in dogs and also attempts to place the relative value of three components of the duodenal juices in the prevention of ulcer formation. The author has attempted to obtain comparable data in his experiments by using a similar technique for all dogs with only

51 Simonds, J. P. Mode of Origin of Experimental Gastric Ulcer Induced by Cinchophen, *Arch. Path.* **26** 44 (July) 1938.

52 DeBakey, M. E. Peptic Ulceration. The Relative Protective Value of the Alkaline Duodenal Juices, *Arch. Surg.* **34** 230 (Feb.) 1937.

minor variations. In each instance the pylorus was severed, and the gastric and duodenal ends were closed. In addition, four variations were introduced: anterior gastroenterostomy, transplantation of the main pancreatic duct of the terminal portion of the ileum, transplantation of the common bile duct of the terminal portion of the ileum and transplantation of both the pancreatic and the common bile duct. In these procedures the production of ulcer was, respectively, 50, 70, 90 and 100 per cent. The author's results, although drawn from relatively few animals, agree with the majority of conclusions stated in the literature—of the constituents of alkali in the duodenal juices, bile has the most significance in preventing the formation of jejunal ulcer, succus entericus is of the least importance, and pancreatic secretion lies between the two.

Hanke,⁵³ by the creation of an external biliary fistula after section of the common bile duct, produced a duodenal ulcer in each of 7 dogs. Factors that were considered in the production of the ulcer were absence of the normal neutralizing action of the bile and a possible diminution of mucosal resistance to the metabolic and hepatic disturbances resulting from the diversion of the bile. Hanke draws the inference that of the many factors involved in the production of a peptic ulcer in man, changes in the biliary secretion may represent an important one.

Volini, Widenhorn and Finlayson⁵⁴ confirmed the previous production of jejunal ulcer in dogs by means of the Exalto and Mann-Williamson methods of diverting the duodenal contents from the stomach and jejunum. The particular finding of interest in their experiments, however, is not elsewhere reported in the voluminous literature on these methods of producing experimental ulcer. These authors noted not only typical acute, subacute or chronic ulcer in the jejunum, but, in addition, in more than half their experimental animals a similar ulcer was found in the excluded duodenum. No satisfactory explanation is suggested, although they feel that trauma can be excluded.

The effect of physiologic hypersecretion with the production of long periods of concentration of hydrochloric acid and pepsin in the gastric juice was studied by Schmidt and Fogelson.⁵⁵ A similar work was carried out by Silbermann in 1927. The present experiments, however, failed to produce ulcer by sham feedings in esophagotomized dogs,

53 Hanke, H. Gastroduodenale Ulcerationen nach totaler Ableitung der Galle, *Arch f klin Chir* **187**:675, 1937.

54 Volini, I. F., Widenhorn, H. O., and Finlayson, U. Experimental Duodenal Ulcer, *Surg, Gynec & Obst* **65** 159, 1937.

55 Schmidt, C. R., and Fogelson, S. J. The Effect of Physiologic Hypersecretion on the Gastroduodenal Mucosa, *Am J Physiol* **120** 87, 1937.

although the animals were studied over much longer periods than in the original experiments and were carried on maintenance and deficient diets, with at times the addition of extra hydrochloric acid introduced through a gastrostomy opening. The conclusion is that acid gastric juice per se is not sufficiently destructive to overcome other factors which inhibit or prevent gastroduodenal ulceration.

Considerable interest has been attached to the relation between ulcer and dietary deficiency. For the most part these studies have been concerned particularly with vitamin C. Numerous reports in the literature have confirmed observations that low blood values for vitamin C are the rule for patients with peptic ulcer, particularly when there has been any tendency to pyloric obstruction with associated malnutrition and prolonged rigid dietary treatment or hemorrhage. Hanke⁵⁶ claims to have noted the frequent occurrence of mucosal ulcer in the pyloric region of the stomach and in the upper portion of the duodenum in guinea pigs kept on a diet deficient in vitamin C. In animals given a diet adequate in vitamin C, such lesions do not occur.

Ingalls and Warren⁵⁷ were among the first to indicate the deficiency of ascorbic acid in the blood plasma of patients with ulcer and to emphasize the probable wisdom of vitamin C therapy. A previous paper by Lanman and Ingalls⁵⁸ brings out the relation between vitamin C deficiency and wound healing. In this study the writers were apparently convinced that in animals receiving a diet deficient in vitamin C abdominal wounds tended to heal less rapidly and less firmly than those in animals receiving a normal diet. Under conditions of ascorbic acid deficiency the wounds tended to rupture spontaneously. Whether vitamin C deficiency has any etiologic relation to the ulcer problem is still a moot point. As noted previously, there is little doubt that low vitamin C values are of frequent occurrence in cases of ulcer, but that such a deficiency has anything to do with the causation of ulcer is still to be determined.

Elder and Emery,⁵⁹ after a careful analysis of the eating habits of 25 patients with ulcer and 25 controls, came to the conclusion that peptic ulcer is not a deficiency disease, in the usual sense of the term.

56 Hanke, H. Experimentelle Erzeugung und Pathogenese von C-Vitaminmangelgeschwüren des Magens, *Klin Wchnschr* **16** 1205, 1937.

57 Ingalls, T. H., and Warren, H. A. Asymptomatic Scurvy. Its Relation to Wound Healing and Its Incidence in Patients with Peptic Ulcer, *New England J Med* **217** 443, 1937.

58 Lanman, T. H., and Ingalls, T. H. Vitamin C Deficiency and Wound Healing. An Experimental and Clinical Study, *Ann Surg* **105** 616, 1937.

59 Elder, M., and Emery, E. S., Jr. Food Habits of Patients with Peptic Ulcer, *Am J Digest Dis & Nutrition* **4** 493, 1937.

A comparison of the dietary histories obtained from these two groups with a theoretically normal diet led them to believe that there is no significant difference, with the exception that the intake of vitamin C is possibly a little low in patients with ulcer. They believe that if peptic ulcer is a deficiency disease the deficiency is an intrinsic factor and is not associated with a deficient intake of food. There is suggestive evidence that vitamin C deficiency may be related to one of the complications of ulcer—hemorrhage. Portnoy and Wilkinson⁶⁰ studied 107 subjects by various methods and showed to their satisfaction that patients with peptic ulcer, especially those with hematemesis, have marked vitamin C deficiency.

In contrast to the analysis made by Elder and Emery, the study made by Bourne⁶¹ on 87 subjects, 42 of whom had ulcer, showed that hospital patients receiving diet for ulcer exhibited a significantly greater degree of capillary fragility than did normal persons or patients with other diseases. However the author is unwilling to conclude that lack of vitamin C is of etiologic significance. Rivers and Carlson⁶² also agree with previous authors that most patients receiving an approved diet for ulcer have an insufficient intake of ascorbic acid. They feel that this is particularly true of patients with repeated hemorrhages, and they speculate as to the possibility that the hemorrhagic factor may be influenced by vitamin C deficiency.

The underlying question of vitamin C deficiency is still not clearly understood, but it is highly probable that the findings represent the results of a deficiency secondary to the original ulcer condition rather than a causative relation to the formation of the ulcer. It is probable that the intelligent administration of vitamin C to patients with ulcer who show a lack of ascorbic acid is a rational therapeutic procedure. There is some reason for believing that it may correct a hemorrhagic tendency and may aid in ulcer healing, although this is far from proved. There is also a suggestion that it may lead to more normal convalescence after a gastrointestinal operation when deficiency exists. In this connection the studies of Reedman⁶³ on the ascorbic acid content of milk are of some interest. From his work it follows that milk alone will not supply sufficient vitamin C in the diet, although it is

60 Portnoy, B., and Wilkinson, J. F. Intradermal Test for Vitamin C Deficiency, *Brit M J* **1** 328, 1938.

61 Bourne, G. Vitamin C Deficiency in Peptic Ulceration Estimated by the Capillary Resistance Test, *Brit M J* **1** 560, 1938.

62 Rivers, A. B., and Carlson, L. A. Vitamin C as a Supplement in the Therapy of Peptic Ulcer, *Proc Staff Meet, Mayo Clin* **12** 383, 1937.

63 Reedman, E. J. Ascorbic Acid Content of Milk, *Canad Pub Health J* **28** 339, 1937.

equally true that it is not normally required to do so. A pint (473 cc) of pasteurized milk may be said to contain 10 mg of cevitic acid.

Hoelzel and Da Costa⁶⁴ carried out extensive observations on rats and mice receiving a diet deficient in protein or in the essential amino acids. Ulceration of the prestomach and main stomach of rats and the duodenum of mice was frequent and was regarded as objective evidence of "protein hunger or amino-acid hunger." Cheney⁶⁵ similarly produced gastric ulcer in chicks by giving a diet devoid of alfalfa and grain. Studies of gastric secretion were carried out on these as well as on control animals, and it was found that chicks with gastric ulcer had hyperacidity. The increased acidity in chicks with ulcer over those without ulcer suggested to the author that it is a result and not a direct cause of the lesion.

Another interesting effect of hypoproteinemia on plasmapheresis is presented in the study of Barden, Ravdin and Frazier⁶⁶. After a Billroth I or II operation dogs were subjected to repeated plasmapheresis and a low protein diet. It was noted that there was marked retardation of the gastric emptying time after the production of hypoproteinemia, and the investigators mention work in progress which also suggests a definite slowing of motility of the small intestine under the same conditions. They explain the reduction in emptying time as possibly being due to nutritional edema of the operative stoma, a hypothesis previously suggested by Jones and Eaton.

PEPTIC ULCER

In a clinical discussion of ulcer an interesting report is presented by Hansen,⁶⁷ who has collected the records of about 14,000 patients with gastric and duodenal ulcer treated medically in certain Danish hospitals since 1900. In the first decade of the century the incidence of ulcer in women was much greater than that in men. In the second decade the numbers were approximately equal for the two sexes, and in the third and fourth decades there was a striking increase in the incidence of ulcer in men, at present about three fourths of all patients being men. The author is unable to explain this remarkable change in relative frequency of the disease.

64 Hoelzel, F, and Da Costa, E. Production of Peptic Ulcers in Rats and Mice by Diets Deficient in Protein, *Am J Digest Dis & Nutrition* 4 325, 1937.

65 Cheney, G. Gastric Acidity in Chicks with Experimental Ulcer, *Am J Digest Dis & Nutrition* 5 104, 1938.

66 Barden, R. P., Ravdin, I. S., and Frazier, W. D. Hypoproteinemia as a Factor in the Retardation of Gastric Emptying After Operations of the Billroth I or II Types, *Am J Roentgenol* 38 196, 1937.

67 Hansen, J. L. Investigations on the Frequency of Peptic Ulcer with Special Regard to Distribution Between the Two Sexes. Fourteen Thousand Cases, *Ugeskr f læger* 99 1145, 1937.

An article by Tomoda⁶⁸ is of interest as indicating the incidence of gastric ulceration in Japan. Four and seven-tenths of over 8,000 autopsies showed gastric ulcer, whereas duodenal ulcer was found in only 0.5 per cent of 6,000 necropsies. In Japan, apparently, gastric and duodenal ulcers occur with much greater frequency in men, while in Europe and America gastric ulcer appears with greater frequency in women.

Comparative data from China, as presented by Chang,⁶⁹ show that the incidence of peptic ulcer in 2,000 consecutive autopsies was 1.7 per cent, a much lower rate than that noted in Japan. The ratio between males and females suffering from this condition was 3.3 to 1.

In 1931 the Division of Vital Statistics in Washington reported a mortality rate for ulcer of the stomach of 4.2 per cent, with the rate for ulcer of the duodenum being only 1.9 per cent, a combined mortality rate of 6.1 per cent. Portis and Jaffé⁷⁰ present the incidence of peptic ulcer in 9,171 consecutive necropsies performed at the Cook County Hospital, Chicago, between 1929 and 1936. There were 457 cases of peptic ulcer, or a total incidence of about 5 per cent. The incidence of peptic ulcer in white subjects was 5.23 per cent and in Negroes 3.5 per cent.

All the aforementioned articles are interesting from the point of view of distribution and occurrence of peptic ulcer. The last article referred to contains many interesting statistical facts regarding the location of ulcer, the relation of ulcer to death and other points of interest. One of the best recent summaries of the problem is that presented by Crohn.⁷¹ It contains nothing new as far as clinical or investigative data are concerned but gives an excellent discussion of the entire problem, it is conservative, convincing and well worth the trouble of reading. Blackford, Smith and Affleck⁷² also present an interesting study based on 916 patients with ulcer seen in private practice. Attention is particularly directed toward a consideration of the problem of hemorrhage and perforation.

68 Tomoda, M. Chirurgische Erfahrungen über Magen- Duodenalgeschwüre auf Grund von 433 Fällen in Japan, *Arch f klin Chir* **190** 134, 1937.

69 Chang, C. C. Acute Perforated Peptic Ulcer. Analysis of Thirty-Seven Operated Cases, *Chinese M J* **52** 161, 1937.

70 Portis, S. A., and Jaffé, R. H. A Study of Peptic Ulcer Based on Necropsy Records, *J A M A* **110** 6 (Jan 1) 1938.

71 Crohn, B. B. Gastroduodenal Ulcer. Etiology, Treatment and End Results, *New England J Med* **218** 148, 1938.

72 Blackford, J. M., Smith, A. L., and Affleck, D. H. Peptic Ulcer Emergencies. A Study of Massive Hemorrhage and Acute Perforations Treated During the Diagnosis of Nine Hundred and Sixteen Private Cases Suffering from Peptic Ulcers, *Am J Digest Dis & Nutrition* **4** 646, 1937.

A rather interesting study of peptic ulcer in pregnancy is presented by Parturiet-Lanegrace⁷³. The paper is a fairly detailed discussion of only 2 patients, but the implications appear to be that pregnancy may have a temporarily favorable effect on the course of peptic ulcer. This is in line with subsequent observations on the use of estrogen as a therapeutic measure.

The absence of peptic ulcer in patients suffering from pernicious anemia does not prove that acid alone is the important etiologic factor in the production of ulcer, but Kahn's⁷⁴ review of 840 cases of pernicious anemia is of interest. For none of this large group of patients with typical Addison's anemia was a diagnosis of chronic peptic ulcer made during the time that the patient was in the hospital. One is inclined to agree with Kahn that at least normal acidity is one of the conditions necessary for the development of chronic peptic ulcer.

The occurrence of ulcer in association with syphilis of the central nervous system has long been noted. The report of Parsons and his associates⁷⁵ is of some interest in this connection. Two hundred patients with syphilis of the central nervous system were compared with a group of 400 other patients in the same hospital. The second group, which included patients with latent syphilis, pulmonary tuberculosis and other diseases not involving the central nervous system, showed an incidence of ulcer which was much higher than that for the first group. Patients with neurosyphilis showed an incidence of ulcer of 10.5 per cent, a figure which is much higher than that reported from other clinics in this country, whereas the control groups showed one of less than 3 per cent. No adequate explanation for the high incidence of ulcer in neurosyphilitic patients is given, and the authors feel that syphilis does not appear to be of true etiologic significance in such cases.

A rare observation was made by Hartung and Warkany⁷⁶ in a case of meningococcic meningitis. The patient was a boy of 6 years who was admitted to the hospital with typical meningitis and who improved under specific therapy. On the twelfth day after the onset of the disease a fatal hemorrhage occurred from an ulcer of the duodenum, which on section showed, among other organisms, groups of

73 Parturiet-Lanegrace, M. Ulceres et grossesses, *Arch d mal de l'app digestif* **26** 1092, 1936.

74 Kahn, J. R. Absence of Peptic Ulcer in Pernicious Anemia, *Am J M Sc* **194** 463, 1937.

75 Parsons, E. H., Plummer, D. E., Ewalt, J. R., and Gaskill, R. C. Peptic Ulcer in Syphilis of the Central Nervous System, *J A M A* **110** 1991 (June 11) 1938.

76 Hartung, C. A., and Warkany, J. Duodenal Ulcer as a Cause of Death in a Case of Meningococcic Meningitis, *J A M A* **110** 1101 (April 2) 1938.

biscuit-shaped gram-negative diplococci, having a structure similar to that of the organisms in the meninges. It is suggested that the ulcer was a result of the meningococcic infection and was analogous to the infection observed in children with ulcer by Gerdine and Hemholtz.

Bloch and Serby⁷⁷ add to the accumulated literature on juvenile ulcer, reporting 5 old cases, 8 new cases and 4 additional cases in which the ulcer started early in life. Although the clinical observations are not new, the authors contributed to a better understanding of a rather infrequent diagnosis. They stress the frequency of a family history of ulcer in many of these cases.

An interesting diagnostic comment is found in the report of Paine and Rigler,⁷⁸ who made observations on 13 patients incidental to the production of diagnostic pneumoperitoneum. They demonstrated on these patients, as well as on 5 cadavers, that at times as small a quantity of gas as 5 cc could be demonstrated roentgenographically in the right subphrenic space. In 17 per cent of 38 cases of perforation of the stomach or duodenum, free gas was observed.

Several articles have been written on the subject of atypical localization of pain in relation to gastroduodenal ulcer. Savignac⁷⁹ reports 14 cases of gastroduodenal ulcer in which the pain was entirely outside the epigastrium. The pain was periodic and was relieved by alkalis and food. Pain was noted in the thorax, in the axillary region and in the precordial region and was similar to angina or the girdle type of pain found in intercostal neuralgia. In 3 cases the pain was located in the dorsolumbar region and in 3 others in the right upper quadrant of the abdomen. In 3 instances the pain was lower in the abdomen. A more general discussion of the analysis of pain in gastroduodenal ulcer is found in an article by Savy and his associates.⁸⁰ The article is analogous to the preceding one and in an excellent discussion brings out the unusual variations in the pain. Mixer⁸¹ calls particular attention to the pain in the back in cases of lesions of the gastrointestinal tract and reports 7 cases of ulcer of the posterior wall

77 Bloch, L., and Serby, A. M. Peptic Ulcer in Children. A Follow-Up Study of Cases Reported Previously and a Report of Additional Cases, *Am J Digest Dis & Nutrition* **4** 15, 1937.

78 Paine, J. R., and Rigler, L. G. Pneumoperitoneum in Perforations of Gastrointestinal Tract, *Surgery* **3** 325, 1938.

79 Savignac, R. La localisation extra-epigastrique de la douleur de l'ulcère gastro-duodenal, *Arch d mal de l'app digestif* **27** 751, 1937.

80 Savy, P., Froment, R., Chapuy, A., and Jeune, M. Les anomalies de la douleur dans l'ulcère gastro-duodenal, *Presse med* **45** 609, 1937.

81 Mixer, W. J. Back Pain in Lesions of the Gastrointestinal Tract with Particular Reference to Duodenal Ulcer, *Am J Digest Dis & Nutrition* **4** 736, 1938.

in which pain in the back was the sole or predominating symptom. These cases are of particular interest since the patient is usually first seen by the orthopedic surgeon or the neurologist and not infrequently the diagnosis of ulcer is postponed until some complication makes it apparent. These anomalies of pain in cases of ulcer are described clinically and experimentally by Jones,⁸² and a correlation is drawn between the experimental production of pain and exact clinical observations.

Among other forms of ulcer therapy, treatment with histidine has received considerable attention. The original experimental results of Weiss and Aron on dogs after the Mann-Williamson operation were apparently definite, and exploitation by pharmaceutical houses rapidly followed. Insufficient substantiation of therapeutic hopes, however, has led to more critical investigation. Furth and Scholl⁸³ state that they were able to corroborate the work of Weiss and his associates, namely, that the cure of an artificially produced ulcer can be accelerated with tryptophan. After much experimentation a method was developed by which injections of histamine produced gastric ulcer in guinea pigs. Whereas ulcers developed in the animals that were treated only with histamine, the simultaneous administration of tryptophan prevented the development. Histidine proved less effective than tryptophan. Practically all other evidence fails to support the idea that histidine is of practical or experimental value. A curious report is that of Jacob and Israel⁸⁴ who show that the ampules of 4 per cent solution of histidine which were utilized for the treatment of gastric ulcers between the years 1933 and 1935 contained approximately 0.1 mg of histamine. Considering that the histamine content might be the effective therapeutic agent, these authors treated a series of patients with daily injections of 0.1 mg of histamine, with complete clinical success. Such results, however, appear to be an excellent example of wishful thinking and do little to clarify the subject.

By far the most conclusive attack on the subject of histidine therapy is that of Sandweiss,⁸⁵ who presents an excellent set of observations. His contribution has a twofold purpose: first, to present clinical data evaluating the results of parenteral therapy in peptic

⁸² Jones, C. M. *Digestive Tract Pain*, New York, The Macmillan Company, 1938.

⁸³ Furth, O., and Scholl, R. *Ueber den Einfluss des Tryptophans und Histidins auf durch Histamin hervorgerufene Magengeschwüre*, *Wien klin Wchnschr* **50** 1353, 1937.

⁸⁴ Jacob, A., and Israel, L. *Le traitement de la crise douloureuse de l'ulcère gastro-duodénal par l'histamine à petites doses*, *Presse med* **46** 210, 1938.

⁸⁵ Sandweiss, D. J. *Comparative Results with Dietetic, Parenteral and Surgical Treatment in Peptic Ulcer*, *J A M A* **108** 700 (Feb 27) 1937.

ulcer and, second, to report on experimental work regarding the protective value of histidine against ulcer in dogs after the Mann-Williamson operation. Of a series of 291 patients with proved ulcer, 118 were treated with various forms of parenteral injections. The remainder were treated by orthodox diet-alkali measures and served as controls. Histidine, vaccine and emetine were the agents used for parenteral injection, and injections of distilled water were administered to a large group of controls (22 patients). From the results obtained Sandweiss concludes that in cases of chronic ulcer, parenteral therapy was of value when the patient failed to respond to diet-alkali management. In this group "parenteral therapy has its chief value as an additional method of treatment." He feels that the psychic factor is largely responsible for the favorable results when they occur. Injections of vaccine apparently were associated with the most satisfactory relief of symptoms, but all the agents employed were beneficial. It is of particular interest that practically 60 per cent of the patients receiving injections of distilled water were relieved of symptoms. The report on the protective value of histidine in experimental studies of ulcer in dogs is made by Sandweiss, Saltzstein and Glazer.⁸⁶ Of 14 dogs treated with histidine after the performance of a Mann-Williamson operation, only 1 failed to show a typical ulcer, and all the control animals showed similar lesions. These authors conclude that histidine had no effect in preventing the production of ulcer under the conditions of the experiment.

Clinical studies by Wilhelmj⁸⁷ and by Upham and Barowsky⁸⁸ support, in the main, the findings of Sandweiss. All agree that recurrences are in no way prevented by treatment with histidine. Upham and Barowsky, like Sandweiss, obtained striking relief of symptoms in a few cases by the use of injections of distilled water alone. A review of these and similar studies leads one to the conviction that histidine, as a therapeutic agent in the treatment of ulcer, is of only temporary value in a limited number of cases and that the favorable results obtained by its use are largely due to the psychotherapeutic effect which follows the parenteral injection of any nonspecific substance.

The medical treatment of peptic ulcer, aside from parenteral injections, has concerned itself with various forms of feeding and with

⁸⁶ Sandweiss, D. J., Saltzstein, H. C., and Glazer, W. S. The Value of Histidine in the Prevention of Experimental Ulcer in the Dog, *Am J Digest Dis & Nutrition* **4** 20, 1937.

⁸⁷ Wilhelmj, E. W. Further Observations of the Histidine Treatment of Peptic Ulcer, *Ann Int Med* **10** 1365, 1937.

⁸⁸ Upham, R., and Barowsky, H. A Clinical Investigation of Histidine Therapy in Cases of Peptic Ulcer, *J A M A* **109** 422 (Aug 7) 1937.

newer preparations for the neutralization or adsorption of hydrochloric acid. An ingenious combination of frequent feedings of milk combined with alkali has been devised by Wosika,⁸⁹ who attempts to control gastric acidity by the use of tablets of alkalinized powdered skimmed milk. Comparative studies were made on a group of patients with successive regimens, consisting of (1) feedings of whole milk and cream alternating with those of standard Sippy powders, (2) feedings of milk and cream alternating with those of powdered whole milk mixed with the same powders and given as tablets, (3) the same feedings alternating with the taking of tablets of powdered whole milk and a mixture of calcium carbonate and sodium bicarbonate and (4) the same feeding alternating with the taking of tablets of powdered skimmed milk and a mixture of calcium and sodium bicarbonate. Apparently the fourth regimen consistently gave the best control of gastric acidity. For practical purposes the use of tablets composed of powdered milk and alkali provides convenience without excessive expense. To obviate the occasional danger of producing alkalosis, several preparations have been studied, all of which aim at neutralizing or adsorbing gastric acidity without altering the p_H of the blood. The effect of magnesium trisilicate has been studied by Mann.⁹⁰ Hourly feedings were combined with the administration on the half hour of 3.5 Gm of the drug. Specimens of the stomach contents were tested at every first and third quarter hour, and practically no free acid could be demonstrated. In vitro studies indicated that acidity was controlled both by adsorption and by neutralization, in the ratio of 2 to 7. Levin⁹¹ also advocates the use of synthetic hydrated magnesium trisilicate because of its prolonged adsorbent action.

Geréb and Korossy⁹² discuss the use of a buffer preparation on the acidity and alkalinity of the stomach. They use a mixture of sodium biphosphate and sodium bisulfate in a ratio of 86 to 14. The preparation is given in doses of 1 Gm at varying intervals. The result of the administration of this preparation is to acidify the urine. Relief was obtained in about 80 per cent of the cases in which it was tried. Laszlo,⁹³ also of Budapest, reports on the use of the product

89 Wosika, P. H. The Control of Gastric Acidity in Peptic Ulcer by Alkalinized Powdered Skimmed Milk Tablets, *Am J M Sc* **195** 676, 1938.

90 Mann, W. N. Experiments on the Neutralization of Hydrochloric Acid by Magnesium Trisilicate, *Guy's Hosp Rep* **87** 151, 1937.

91 Levin, M. B. Peptic Ulcer Therapy, *Am J Digest Dis & Nutrition* **4** 574, 1937.

92 Gereb, I., and Korossy, F. Therapy of Gastric Secretory Disturbances with Buffer Compounds, *Gyogyászat* **74** 146, 1934.

93 Laszlo, G. Clinical Experiments with a Buffer That Normalizes the Hydrogen Ion Concentration of the Stomach, *Rev Gastroenterol* **4** 35, 1937.

He obtained amelioration of symptoms in three fourths of a series of 96 patients suffering from ulcer and other gastric disorders

The search for the perfect antispasmodic still continues Einhorn⁹⁴ substituted diphenylacetyl-diethylaminoethanolester hydrochloride for belladonna in a small group of cases of gastrointestinal disorders Toxic effects were not noted, and when distress or pain was not associated with an inflammatory reaction, satisfactory relief of symptoms was obtained Several other investigators have made use of this new preparation, but as yet it has not been sufficiently tested to warrant further comment

Two studies which yielded negative results are of interest Warren, Friend and Emery⁹⁵ subjected 5 patients with ulcer, who volunteered for the experiment, to a diet similar to that used by Goldberger and Wheeler to produce pellagra The basis for such an experiment lay in the fact that patients with pellagra frequently are found to have hypoacidity or anacidity Two of the subjects followed the diet for an average of fifty-nine days and 1 for one hundred and twenty-five days Gastric analyses performed every two or three weeks failed to indicate any change in gastric acidity, and it was concluded that such a dietary method of managing ulcer is obviously impracticable as well as unproductive of results Emery and Schnitker⁹⁶ also administered bile to patients with peptic ulcer The basis of such an experiment was the fact that diversion of bile from the duodenum in animals is an important detail in the experimental production of ulcer A total of 40 patients were treated with desiccated ox bile over periods as long as two years A satisfactory result occurred in only 52.5 per cent of the cases, a proportion that is not much better than that of spontaneous cures, as Emery aptly remarks He also concludes that his results seem to rule out a disturbance in the biliary secretion as a cause of peptic ulcer in man

An inconclusive article but one of possible physiologic interest is presented by Korbsch,⁹⁷ who treated 4 patients with gastric ulcer with injections of an estrogen substance Excellent healing of the ulcer was observed gastroscopically after twenty-four, thirteen, twenty-

94 Einhorn, M The Use of a New Antispasmodic Drug in Gastro-enterology A Preliminary Report, *Am J Digest Dis & Nutrition* 5 121, 1938

95 Warren, H A, Friend, D A, and Emery, E S, Jr The Treatment of Peptic Ulcer by the Diet of Goldberger and Wheeler, *Am J Digest Dis & Nutrition* 4 495, 1937

96 Emery, E S, Jr, and Schnitker, M A Peptic Ulcer The Effect of the Administration of Bile on the Behavior of the Disease, *Ann Int Med* 10 2007, 1937

97 Korbsch, R Heilungen von Magenulzera durch Follikelhormon-Injektionen, *Deutsche med Wchnschr* 63 599, 1937

eight and sixteen days, respectively. One patient was said to have been resistant to other forms of therapy, and a second responded without the addition of dietary measures. Unfortunately the series is so small as to admit of no conclusions, particularly when it is remembered that spontaneous cure is extremely frequent. Favorable results have been reported for many types of parenteral therapy, and the comments of Sandweiss and others regarding injection methods of treatment must always be borne in mind in the evaluation of results such as are reported in this paper. Furthermore, another contribution by Sandweiss is pertinent in any consideration of the effect of hormones on the healing of ulcer. This article, by Sandweiss, Saltzstein and Farbman,⁹⁸ presents the results of injecting preparations of estrogenic substance (esterone, or theelin) and gonadotropic substance from the urine of pregnant women (antuitrin S) in dogs after the Mann-Williamson operation. The work was inspired by the clinical observation that pregnancy appears to have a beneficial effect on peptic ulcer. Twelve untreated animals all died of typical jejunal ulcer. Unlike the results claimed by Korbisch, all the 15 dogs that received injections of estrogenic substance died and showed ulcers similar to those noted in the controls and without any evidence of healing. Eight of a group of 15 animals treated with the gonadotropic substance which eventually died of inanition failed to show any evidence of ulcer formation. Seven died with jejunal ulcer, but 4 of these 7 showed microscopic evidence of healing. The author concludes in a rather cautious manner, that the injection of large amounts of the gonadotropic substance may have been responsible for the favorable results.

The importance of considering psychologic factors in the treatment of peptic ulcer has been frequently noted. Two intelligent papers have been written on this aspect of the problem recently. Chappell, Stefano, Rogerson and Pike⁹⁹ carried out an interesting experiment on a group of patients with ulcer. In addition to routine dietary measures, evening lectures were given to these patients in order to provide a better understanding of such factors as worry, expenditure of effort, psychosomatic relation and self assurance. A control group were handled by dietary measures alone. Over a three year period the first group of patients responded to treatment better in every way than did the controls, and even those who suffered from relapses during this period were able to handle their symptoms more satisfactorily.

98 Sandweiss, D. J., Saltzstein, H. C., and Farbman, A. The Prevention or Healing of Experimental Peptic Ulcer in Mann-Williamson Dogs with the Anterior Pituitary-Like Hormone (Antuitrin-S). A Preliminary Report, *Am J Digest Dis & Nutrition* 5 24, 1938.

99 Chappell, M. N., Stefano, J. J., Rogerson, J. S., and Pike, F. H. The Value of Group Psychological Procedures in the Treatment of Peptic Ulcer, *Am J Digest Dis & Nutrition* 3 813, 1937.

The paper by Davies and Wilson¹⁰⁰ provides a convincing demonstration of the psychic element in the development of peptic ulcer. A series of 205 patients with ulcer were carefully examined psychologically, and it appeared that in 84 per cent of the cases the symptoms began shortly after some event affecting the patient's work, his finances or the health of his family. One hundred of these patients were compared with an equal number of patients with hernia, Culpin's system of group scoring being used. It was found that a significant majority of the patients with ulcer showed undue tension long before the symptoms of ulcer developed. The conclusion that successful therapy depends on attention to the "whole man," his work and his anxieties as well as his diet, if not original, is nevertheless of great importance, since even a superficial survey of the literature reveals innumerable conclusions as to the specificity or importance of various therapeutic maneuvers with a fine disregard of the known history of this chronic disease.

The management of massive hemorrhage as an incident in the course of peptic ulcer is still a controversial matter. Conservative measures in the treatment of this emergency are undoubtedly indicated in the earlier decades of life. Mortality statistics are still confusing and in part depend on the character of the case under discussion or the type of treatment chosen. Meulengracht's¹⁰¹ latest report on 368 medically treated patients with a mortality of only 1.3 per cent is amazing and indicates that the administration of a full diet to these patients must be considered seriously before what has seemed like a radical departure from accepted methods is discarded. Finsterer's¹⁰² criticism that these represent cases of superficial gastric erosions and gastritis does not seem entirely tenable. Woldman's¹⁰³ small series of patients with massive hemorrhage treated with continuous aluminum hydroxide drip provides a new modification of the already known treatment with continuous milk drip. The fact that all 20 patients responded rapidly and satisfactorily to this treatment loses a little of its importance because of the failure of the author to give the nature of the underlying pathologic process in the different cases. Whether continuous drip methods are more efficacious than the method of Meulengracht will be determined only by prolonged use with large groups of patients. Opposed to such conservative measures are various surgeons

100 Davies, D. T., and Wilson, A. T. M. Observations on the Life-History of a Chronic Peptic Ulcer, *Lancet* **2** 1353, 1937.

101 Meulengracht, E. Weitere Erfahrungen über die Behandlung massiver Magenblutungen ohne Beschränkung der Nahrungszufuhr, *München med Wchnschr* **84** 1565, 1937.

102 Finsterer, H. Indikationsstellung zur operativen Behandlung der akuten schweren Magenblutung, *Wien med Wchnschr* **88** 201, 1938.

103 Woldman, E. E. The Treatment of Hematemesis and Melena by a Continuous Aluminum Hydroxide Drip, *Am J M Sc* **194** 333, 1937.

of known standing. The most radical of all the proponents of surgical treatment of bleeding ulcer is Finsterer¹⁰². In a recent summary of the subject he reiterates his conviction that gastric resection is the method of choice in practically all cases of massive gastric hemorrhage, including even known cases of cirrhosis, provided any gastric symptoms accompany the disease of the liver. Only if bleeding appears suddenly, without preceding symptoms, does he advise medical treatment. Between these two extremes lie the views of the majority of those interested in this difficult clinical problem. An excellent summary of the question is contained in a recent editorial in *The Journal of the American Medical Association*¹⁰⁴. In all probability the crux of the situation is the age of the individual patient. With rare exceptions, patients under the age of 45 or 50 run an almost negligible risk when treated by careful medical procedures. After that age surgical intervention must not infrequently be considered as the logical form of treatment, the type of operation depending on the experience of the individual surgeon. Even in older patients conservative measures are usually indicated. When operation is involved, however, the decision to operate had best be made within the first forty-eight hours after bleeding, as suggested by Finsterer,¹⁰² Allen¹⁰⁵ and others. Excellent reviews of the clinical aspects of gastric hemorrhage are presented by Jankelson and Segal,¹⁰⁶ by Blackford, Smith and Affleck⁷² and others.

There is still no absolute agreement as to the proper surgical treatment for ulcer, even in the event of perforation. Numerous reports from various parts of the world are of interest, largely because of the differences of opinion that are shown. McCreery¹⁰⁷ expresses what is probably the point of view commonly held in this country in a report of 170 cases of perforated gastric or duodenal ulcer. He advocates simple closure in most instances, and this opinion is confirmed by Boneo and Ramirez,¹⁰⁸ of Buenos Aires, Chang,⁶⁹ of Peiping, and Lemberg¹⁰⁹ and Sosnyakov,¹¹⁰ of Leningrad, to cite articles from widely scattered

104 The Bleeding Peptic Ulcer, editorial, J A M A **110** 1491 (April 30) 1938

105 Allen, A W. Acute Massive Hemorrhage from the Upper Gastro-Intestinal Tract, with Special Reference to Peptic Ulcer, Surgery **2** 713, 1937

106 Jankelson, I R, and Segal, M S. Massive Hemorrhage from Peptic Ulcer, New England J Med **219** 3, 1938

107 McCreery, J A. Perforated Gastric and Duodenal Ulcer, Ann Surg **107** 350, 1938

108 Boneo, G, and Ramirez, E A. Perforacion gastroduodenal, observaciones de Guardia. 85 casos, Semana med **1** 104, 1938

109 Lemberg, D A. Perforating Gastroduodenal Ulcers, Novy khir arkhiv **37** 191, 1936

110 Sosnyakov, N G. Gastroduodenal Perforation. One Hundred and Twenty-One Cases, Novy khir arkhiv **39** 74, 1937

points Judin,¹¹¹ of Moscow, however, believes with other more radical surgeons that partial gastrectomy is the method of choice Heim,¹¹² of Berlin, on the basis of 283 cases, comes to a similar conclusion Judin's large series of 426 patients who were subjected to subtotal gastric resection, with a mortality of only 7.8 per cent, convinces one of his surgical skill, however, rather than of the soundness of his judgment in choosing such a radical procedure

There is a similar difference of opinion as to the surgical method of choice in uncomplicated ulcer Articles by Abell¹¹³ and Walters¹¹⁴ are representative of those advocating the simplest type of operation for duodenal ulcer, namely gastroenterostomy Subtotal gastrectomy as a routine procedure for duodenal and gastric ulcer has met with the approval of many continental surgeons, following the work of Finsterer and Hoffmeister This more radical procedure is chosen by many and articles by Manizade,¹¹⁵ Hustinx,¹¹⁶ Mouchet¹¹⁷ and Neuman,¹¹⁸ for example, proclaim the benefits of using this method The middle of the road opinion is well summarized in an article by Marshall and Kiefer,¹¹⁹ who point out correctly that most cases of ulcer offer primarily medical problems, in the event that surgical intervention is necessary, the problem is always an individual one, and the type of operative approach must be decided by balancing the probable risks against the probable benefits Finsterer¹²⁰ reports a series of 200 unusual cases of jejunal ulcer, with a mortality of only 11.1 per cent after radical operation in 180 cases of uncomplicated jejunal ulcer The mortality for the entire series was 15.3 per cent

111 Judin, S. S. Partial Gastrectomy in Acute Perforated Peptic Ulcer, *Surg., Gynec. & Obst.* **64** 63, 1937

112 Heim, W. Nachuntersuchungen operierter perforierter Magen- und Zwölffingerdarmgeschwüre, *Deutsche med. Wchnschr.* **63** 1321, 1937

113 Abell, I. The Surgical Treatment of Peptic Ulcer, *Ann. Int. Med.* **11** 762, 1937

114 Walters, W. Should Gastric Resection Be Done for Duodenal Ulcer? *Surgery* **2** 759, 1937

115 Manizade, M. D. Zur Frage der Anämie nach Magenresektion, *Wien klin. Wchnschr.* **50** 1455, 1937

116 Hustinx, E. Le traitement de l'ulcère du duodénum par la résection gastroduodénale: sa technique, ses résultats immédiats et éloignés, *Arch. franco-belges de chir.* **35** 305, 1936

117 Mouchet, A. Quelques réflexions sur la gastrectomie dans l'ulcère gastroduodénale, *Paris méd.* **2** 81, 1937

118 Neuman, F. Le traitement des ulcères gastriques et duodénaux par la gastrectomie, *Bull. Acad. roy. de med. de Belgique* **1** 417, 1936

119 Marshall, S. F., and Kiefer, E. D. Partial Gastrectomy for Gastric or Duodenal Ulcer, *J. A. M. A.* **109** 1341 (Oct. 23) 1937

120 Finsterer, H. Erfahrungen bei über 200 selbst ausgeführten Radikaloperationen wegen *Ulcus pepticum jejuni*, *Arch. f. klin. Chir.* **189** 597, 1937

It is of interest that serious anemia is of infrequent occurrence after subtotal gastrectomy. Manizade¹¹⁵ made a study of 40 patients who were examined from five to twelve years after operation. In all cases extensive resection, involving two thirds of the stomach, had been performed. Examination of the blood showed that in 36 of the 40 cases the red blood cell count was over 4,500,000 and the hemoglobin value over 80 per cent (Sahli). Two patients showed a slight degree of normochromic anemia. Two patients, or 5 per cent of the entire series, were found to have hyperchromic anemia, with a red blood cell count in the vicinity of 2,000,000. One of these patients, prior to operation, showed an abnormal blood picture, suggesting an early stage of pernicious anemia, and gave the history that her mother had died of pernicious anemia. These findings are entirely consistent with comments made by other investigators who have followed the behavior of the blood after radical gastric operations. It is obvious that the danger of the development of a serious form of anemia after the removal of a large portion of the stomach is not important. Factors predisposing to the development of such a condition may exist before operation, and gastric resection rarely initiates the appearance of primary hyperchromic anemia. Blood regeneration after hemorrhage from an ulcer was considered by Schjødt,¹²¹ who found that age, sex and the form of bleeding (melena or hematemesis) made little or no difference in the rate of recovery from the loss of blood. He did find, however, that regeneration was much slower when the patient was treated with a restricted diet, such as the Sippy regimen, than with a full diet, as suggested by Meulengracht. With a Meulengracht regimen he found that the lower the initial blood level after hemorrhage, the more rapid the response to therapy, whereas the converse was true for patients with a restricted dietary intake. Transfusion obviously was necessary in certain cases but did not hasten blood regeneration—a point that has frequently been noted.

A discussion of the subject of gastrojejunal fistula by Rife¹²² presents no new information concerning one of the complications of gastric operations but gives a complete and thoughtful review of the subject.

Few additions have been made to the already existing mass of information on carcinoma of the stomach. Castleman¹²³ contributes

121 Schjødt, E. The Influence of Sex, Age, Form of Hemorrhage, Treatment and Complications on Erythrocyte Regeneration After Hematemesis and Melena from Peptic Ulcer, *Am J M Sc* **193** 327, 1937.

122 Rife, C S. Gastrojejunal Fistula, *Am J Surg* **40** 73, 1938.

123 Castleman, B. Extension of Gastric Carcinoma into the Duodenum, *Ann Surg* **103** 348, 1936.

the important pathologic observation that not infrequently cancer of the lower end of the stomach extends beyond the pylorus into the duodenum. Such a finding is an indication that ample resection of the first portion of the duodenum, whenever possible should accompany resection of the gastric neoplasm. Balfour¹²⁴ has reviewed the subject, basing his observations on a series of 4,793 patients operated on at the Mayo Clinic. In 2,112 cases the growth was removed as a palliative measure or in the hope of a cure, which a mortality of 13.9 per cent. Several points of interest are mentioned. For the most part, the percentage of five-year survivals was larger for the older patients and for those who had a longer story of preoperative symptoms. The nearer the growth was located to the pylorus, the more difficult it was to obtain a successful surgical result. Patients with a carcinomatous growth graded 1 or 2 showed 63 per cent survival after five years and 55 per cent survival after ten years, those with growths graded 3 or 4 showed only 20 per cent survival at the end of the five year period. These statistics offer rather convincing evidence that radical surgical treatment is justified, even in what seem to be rather hopeless cases of gastric cancer.

Shifflett¹²⁵ presents a review of diverticulum of the stomach and considers that it may be of definite clinical significance after other conditions have been ruled out as potential factors in causing the patient's symptoms. In a series of 786 roentgenograms of the stomach and 887 similar studies of the colon, the occurrence of diverticula was as follows: colon, 4.96 per cent, duodenum, 3.74 per cent, esophagus, 0.79 per cent, stomach, 0.65 per cent, and small bowel, 1 case. He reviews his own 5 cases and 38 reported in the literature, one third of the patients had definite symptoms of burning or vomited.

Little new has been contributed in the way of roentgenologic studies of peptic ulcer. However, an article by Hampton¹²⁶ presents a satisfactory technic for the demonstration of a dangerously bleeding ulcer. Whenever compression or palpation is contraindicated or impossible, it is now possible by this method to make a profile, relief and double contrast examination of the posterior wall of the stomach, the pyloric valve and the posterior wall of the duodenum. The examination can be carried out when there is active bleeding with little if any additional risk and can thus provide information that is frequently essential to

124 Balfour, D. C. Factors of Significance in the Prognosis of Cancer of the Stomach, *Ann Surg* **105** 733, 1937.

125 Shifflett, E. L. Diverticula of the Stomach, *Am J Roentgenol* **38** 280, 1937.

126 Hampton, A. O. A Safe Method for the Roentgen Demonstration of Bleeding Duodenal Ulcers, *Am J Roentgenol* **38** 565, 1937.

the proper planning of therapeutic measures. The report of Unger and Poppel¹²⁷ calls attention to an error in roentgenographic interpretation that may lead to improper steps in the treatment of a known ulcer. They report on a patient with gastric ulcer who was operated on because a persistent niche was demonstrated roentgenographically, despite symptomatic cure after five weeks of treatment. At operation the ulcer was found to be completely healed. The conclusion that roentgenologic findings are in themselves insufficient evidence on which to base a therapeutic decision is obvious, but the warning is timely. Bignami¹²⁸ presents a rather interesting review of the subject of extrabulbar duodenal ulcer. Among 400 cases of duodenal ulcer the author found 18 cases in which there was extrabulbar location. From his own experience and from the findings of others, the writer believes that this type of ulcer occurs most frequently in the convexity of the duodenal loop and in the suprapapillary region. He considers that the demonstration of a niche at roentgen examination is the only infallible evidence of an extrabulbar ulcer, although with modern relief methods it is probably true that the demonstration of a crater is of equal diagnostic importance. The chief value of the article is that it stresses the occurrence of a lesion that is all too frequently missed by routine roentgenographic methods of study.

GASTROSCOPY

The increasing number of articles on this subject is convincing evidence of the interest as well as the importance of gastroscopic examination as a diagnostic procedure. In this country, in particular, the enthusiastic reception of a new diagnostic aid is the undoubted forerunner of a host of articles, few of which will be written in a sufficiently critical spirit to warrant their appearance. It will be necessary for some time to warn against undue enthusiasm and against conclusions drawn from improperly controlled material. The wise counsel of Henning and Schindler must be repeated many times before a satisfactory correlation is made between gastroscopic findings and clinical symptoms. Normal variations, which are extremely wide and still are not fully appreciated, must be conscientiously studied and classified before an adequate understanding is obtained of the many changes in the appearance of the gastric mucosa. There is little question, however, that such understanding will come and that gastroscopic examination will provide increasingly valuable assistance in the study of gastric disease and gastric physiology.

127 Unger, A. S., and Poppel, M. H. Healing of Gastric Ulcer with Persistence of Niche Roentgenographically, *Am J Roentgenol* **39** 592, 1938.

128 Bignami, G. Rilievi sopra un nuovo gruppo di osservazioni di ulcera del duodeno in sede extrabulbare, *Boll d Soc med-chir*, Pavia **51** 401, 1937.

The outstanding work on gastroscopy during the period of this review is the book by Schindler¹²⁹. A detailed review is unnecessary at this time, but the volume has almost universally received favorable comment. Schindler discusses the history of the subject with anatomic notes, the mechanical problems of technique and orientation, the appearance of the normal stomach and the appearance in cases of functional and pathologic disturbances. He repeatedly emphasizes the most important point, that gastroscopic examination is an adjunct to roentgen examination and that both methods are essential to an accurate diagnosis of gastric disorders. Ninety-six excellent color plates add greatly to the usefulness of this important volume.

Schindler¹³⁰ calls attention to the type of tip to be used on the flexible gastroscope. With other workers, he believes that the original sponge tip produces too much friction and may result in perforation of the gastric wall. The rubber finger tip appears to be preferable, in that it directs the instrument more satisfactorily, and it is safer, because it produces no friction. Korbsch¹³¹ prefers his new small rigid gastroscope, with a diameter of only 6 to 7 mm, to the Wolf-Schindler instrument. Halmös¹³² agrees in choosing this instrument, which gives a smaller picture but a larger field. He claims to have noted finer details of gastric markings, small hemorrhages and early mucosal hypertrophy that could not be observed with the flexible scope. This is not in agreement with the opinion of nearly all other observers, who believe that the flexible Wolf-Schindler instrument is safer and more satisfactory. Kiriwara and his co-workers¹³³ have attempted to improve on the Wolf-Schindler gastroscope by adding a mechanism by which the tip can be bent at will. The mechanism is described and it is possible that the authors' claims will be justified. They state that with this modification they can obtain a much better view of the pyloric end of the stomach.

Contrary to the experience of most observers, Borland¹³⁴ has found that there are no true "blind spots" and thinks that by proper manipu-

129 Schindler, R. *Gastroscopy: The Endoscopic Study of Gastric Pathology*, Chicago, University of Chicago Press, 1937.

130 Schindler, R., and Renshaw, J. F. Experimental Study with Certain Tips Used on the Wolf-Schindler Flexible Gastroscope, *Am J Digest Dis & Nutrition* **3**: 747, 1936.

131 Korbsch, R., cited by Halmös¹³².

132 Halmös, R. Die Magenspiegelung mit den dunnkalibrigen Instrumenten nach Korbsch, *Med Klin* **33**: 702, 1937.

133 Kiriwara, S., Nakayama, H., Saloh, Y., Konda, Y., and Ito, I. Japanese Improved Flexible Gastroscope, *Nagoya J M Sc* **11**: 1, 1937.

134 Borland, J. L. Present Status of Flexible Tube Gastroscopy, *South M J* **30**: 310, 1937.

lation of the instrument, by changing the position of the patient and by observing the peristaltic wave, all portions of the stomach can be brought into view. His suggestions as to gastroscopic technic are of interest, but it must be admitted that a satisfactory examination of certain parts of the stomach in particular cases is extremely difficult. These portions are notably the lesser curvature near the pylorus in a J-shaped stomach, the greater curvature, at a point where the tip of gastroscope impinges, and occasionally high up on the posterior wall where the objective lens is in immediate contact with the gastric mucosa.

A point of importance is made by Schindler¹³⁵ in an article on the anatomy of the stomach. He calls attention to the division of the interior of the stomach into the body and the antrum, distinctly separated by the characteristic cordlike muscular antial sphincter. This is an important gastroscopic landmark and is formed, he believes, by a circular contraction of the muscularis propria, which is crossed by oblique folds of mucosa. He also calls attention to the mucosal folds as observed gastroscopically. These are most marked on the posterior wall, usually absent on the lesser curvature and always absent from the antrum. They do not seem to correspond completely with the roentgenographic relief markings.

Studies of gastric physiology as observed through the gastroscope are few. Bruhl¹³⁶ has studied the effect of externally applied heat and cold on the appearance of the stomach. The application of a hot water bottle to the epigastrium always increased peristaltic activity and usually caused marked reddening of the gastric mucosa. Opposite effects were noted with the application of cold. These findings are entirely in accord with the studies on gastric motility previously alluded to. In 1,700 examinations Chevallier, Moutier and Debrey¹³⁷ observed 4 instances of sudden changes in the color of the gastric mucosa, which they can explain only on the basis of a vasomotor disturbance. They believe that these changes are not due to the effect of drugs or the presence of the instrument. The changes in color were striking.

The clinical value of gastroscopic examination is undoubtedly greatest in its fairly exact determination of the source and the character of gastric bleeding. Chevallier and Moutier¹³⁸ have made an

135 Schindler, R. Gastroscopic Observation Concerned with the Gross Anatomy of the Stomach, *Am J Digest Dis & Nutrition* **3** 149, 1936.

136 Bruhl, W. Gastroskopische Untersuchungen über die Wirkung thermischer Hautreize auf den Magen, *Deutsche med Wchnschr* **63** 129, 1937.

137 Chevallier, P, Moutier, F, and Debrey, C. Perturbations vasomotrices segmentaires constatées à l'endoscopie gastrique, *Arch d mal de l'app digestif* **27** 1042, 1937.

138 Chevallier, P, and Moutier, F. Les hemorrhagies gastriques et leur controle endoscopique, *Presse med* **44** 1814, 1936.

excellent report on hemorrhage from the stomach. They point out that the normal gastric mucosa does not bleed on the introduction of the gastroscope. Artificial hemorrhages may be due to abnormal fragility of the mucosa, a point carefully noted by Baumel,¹³⁹ who calls attention to the fragility of the mucosa in superficial gastritis and its tendency to bleed easily, especially on the lesser curvature and on the posterior wall near the cardia. Chevallier and Moutier comment on the fact that gastric purpura may exist with or without external manifestations. Mucosal eruptions resemble the cutaneous lesions, and macular ecchymoses may be found in all parts of the stomach. Gastric hematoma is rare, but 1 case was noted (a case of splenomegaly). Varicose veins have also been observed in a stomach with an atrophic mucosa, the patient in this instance having had two or three hemorrhages a year. Gastroscopic examination showed the frequency of ulcer which is silent clinically and roentgenologically but which is capable of bleeding. Such a hemorrhagic lesion is most frequently encountered on the lesser curvature at the angle of the stomach. Chevallier¹⁴⁰ has also expressed the conviction that ulcer is not a frequent cause of bleeding. He thinks that the usual cause is found in a fleeting hemorrhagic lesion which may be near to or at a distance from an actual peptic ulcer. In other words, he feels that even though an ulcer is present at the time of a gastric hemorrhage, it may well be inactive and the bleeding may be due to an area of active gastritis. Such an area may present a localized spot with fine ecchymotic speckling, sometimes hardly discernible. He believes that bleeding from cancer is usually due to concomitant gastritis of the hemorrhagic or erosive type. He finds submucosal hemorrhage fairly frequent in hepatic insufficiency but rare in early cirrhosis and exceptional in advanced cirrhosis. In certain cases of cholecystitis and chronic appendicitis accompanied by hematemesis, gastroscopic examination has demonstrated discrete and fleeting changes in the gastric mucosa, which, Chevallier is sure form the anatomicopathologic basis of the bleeding. Granted the correctness of the underlying diagnosis, these findings are of interest in relation to the cases of disease of the gallbladder with hematemesis reported a few years ago by White. Benedict¹⁴¹ has also emphasized the clinical importance of gastritis as a cause of massive bleeding from the stomach. Although

139 Baumel, J. La gastroscopie en pathologie gastrique gastrites—ulcuses—diverticules—cancer—tumeurs bénignes, Bronchoscop, œsophagoscop et gastroscop, April 1937, p. 105.

140 Chevallier, R. Les hemorrhagies gastriques. Etude gastroscopique, Lyon med **159** 3, 1937.

141 Benedict, E. B. Hemorrhage from Gastritis. A Gastroscopic Study, Am J Digest Dis & Nutrition **4** 657, 1937.

such an observation is not new, it has received insufficient notice until recently. The importance of his observations lies in the fact that frequently a gastric hemorrhage of alarming proportions may occur with no clinical or roentgenographic indication of its source. He presents gastroscopic and roentgenographic studies of 20 cases of acute or chronic gastritis with hemorrhage. The only likely and demonstrable source of the bleeding in these cases was found gastroscopically to be superficial or hypertrophic gastritis, often with one or more erosions in the gastric mucosa. In these cases the excessive use of alcohol seemed to be a frequent factor in the precipitation of the hemorrhage.

As clearly emphasized by Henning and Schindler, the exact diagnosis of gastritis as a cause of clinical symptoms demands long experience in gastroscopic studies and excellent clinical judgment. The classification of this condition is still far from clear, but to most observers Schindler's classification appears to be the simplest and therefore the most practicable. Certainly at present too detailed a nomenclature will end only in confusion, although it must be admitted that any classification may at times be entirely unsatisfactory. Schindler,¹⁴² in attempting to correlate the histologic and gastroscopic findings in chronic gastritis, concludes that a positive microscopic picture does not prove the existence of clinical "disease" of the stomach. Almost every adult shows some interstitial changes in the stomach as compared with the histologic picture in the newborn. Obviously, prolonged observation is needed to harmonize anatomic and gastroscopic findings in a disease the clinical significance of which is imperfectly understood. On the other hand, as indicated in the careful report of Schloss, Ettinger and Pratt,¹⁴³ gastroscopic study frequently provides an explanation for symptoms in certain cases in which the condition has been diagnosed as normal or psychoneurotic by the usual procedures. Although the subject is far from new, the report by Ansprenger and Kirklin¹⁴⁴ provides an excellent discussion of the limitations of the roentgenologist in attempting to make a diagnosis of gastritis. Serious changes seen gastroscopically may completely escape roentgenographic detection. In only a small proportion of cases of gastritis can the diagnosis be made by the roentgenologist. Mucosal atrophy cannot be seen roentgenographically. The most important and most frequent roentgenologic

142 Schindler, R. Relationship of Histologic and Gastroscopic Findings in the Diagnosis of Chronic Gastritis, *Am J Digest Dis & Nutrition* **3** 153, 1937.

143 Schloss, J. Ettinger, A., and Pratt, J. J. Diagnosis of Diseases of the Stomach by Gastroscopic and X-Ray Relief Studies, *Am J M Sc* **193** 171, 1937.

144 Ansprenger, A., and Kirklin, B. R. Roentgenologic Aspects of Chronic Gastritis. Critical Analysis, *Am J Roentgenol* **38** 533, 1937.

sign of gastritis is the presence of localized rigid, irregular, hypertrophic mucosal folds. Wartlike granulations, mucosal erosions that can be demonstrated *en face* and pseudopolypous formations are so infrequently demonstrable that they are of relatively little importance in the diagnosis of gastritis. Tangential projections on or near the lesser curvature, such as have been described, can be observed more frequently. When found they constitute absolute proof of the presence of ulcerous gastritis. Indirect signs must be interpreted with great caution and are significant only when associated with more definite findings. In addition to these comments of Ansprenger and Kirklin, one may say that even when the roentgenographic diagnosis of gastritis is correct, it cannot be as complete as that made with the aid of the gastroscope. Negative roentgenographic findings are of no value in the making of this particular diagnosis.

Schindler, Ortmyer and Renshaw¹⁴⁵ have attempted to classify the symptoms of chronic gastritis. They state that 50 per cent of the patients with superficial gastritis show periodic distress and 30 per cent constant distress, usually epigastric burning, gnawing, dull pressure or pain. Two thirds of these patients obtain relief with alkali and one third with food. In hypertrophic gastritis, half the patients also show periodic distress, with severe pain in 25 per cent and dull burning or gnawing in the remainder, usually one to three hours after meals. In 50 per cent of such cases, food or alkali gives relief. The predominance of males with hypertrophic gastritis is striking, the ratio being 22 to 1 in the cases studied. Antral gastritis was noted only twice. No correspondence was noted between the extent and severity of the gastritis observed gastroscopically and the severity of the symptoms. Schindler¹⁴⁶ reports an unusual case of hypertrophic gastritis with ulceration in which roentgen therapy was given. This patient was observed over a period of twelve years. The diagnosis could be made only by gastroscopic study, as roentgenographic relief study did not demonstrate marked changes in the mucosa. A gastroscopic study was made sixty-five times in this case. Ulceration and pain were present, in spite of all the usual methods of treatment. Although marked gastritic changes were present, with superficial ulceration, true peptic ulcer did not develop. High voltage roentgen therapy caused severe, acute, purulent gastritis, with subsequent regeneration of an essentially normal mucosal membrane. It is of interest to note, however, that one year later atrophic gastritis developed. At present it is probable that

145 Schindler, R., Ortmyer, M., and Renshaw, J. F. Chronic Gastritis, *J. A. M. A.* **108** 465 (Feb. 6) 1937.

146 Schindler, R. Chronic Hypertrophic Ulcerative Gastritis Treated by Coutard's Method of Roentgen Therapy, *Am. J. Digest. Dis. & Nutrition* **3** 751, 1937.

no one is in a position to evaluate the relation between chronic gastritis and peptic ulcer, and any conclusions as to whether or not gastritis is the underlying cause of ulcer are purely speculative. Einhorn,¹⁴⁷ in a clinical study, says he believes that ulcer is not the result of gastritis. His article loses much of its force since his conclusions are not based on gastroscopic evidence but his argument that the acidity in chronic gastritis is low, in contrast to the high acidity in peptic ulcer is probably sound. Taylor¹⁴⁸ in a gastroscopic study, comes to the opposite conclusion. In discussing the question of postoperative gastritis he assumes that some of the inflammatory process was present before the operation and was therefore the cause of the peptic ulcer.

In this connection there are numerous studies of the common condition of postoperative gastritis. Such observations are gradually accumulating evidence that is important as regards the indications for surgical treatment of ulcer and as an aid to the explanation of many postoperative symptoms. Schindler and Giere¹⁴⁹ discuss the relation of the gastroscopic findings to gastric operations and emphasize the importance of gastroscopic study in differentiating between benign and malignant disease, in determining the operability of carcinoma and in making an early diagnosis of carcinoma. Although they state that postoperatively the stoma can usually be seen, they point out the difficulties frequently encountered. A relatively normal gastric mucosa is seen in only about 10 per cent of cases postoperatively. Among the postoperative gastroscopic findings chronic gastritis is most common, but recurrent ulcer, jejunal ulcer, hemorrhagic erosions and silk sutures which have cut through the mucosa are also found. In this article Schindler again calls attention to the pylorus-like rhythmic activity of the artificial stoma. Carey¹⁵⁰ has contributed an article on the postoperative appearance of the stomach, as a result of his findings he believes that every patient who is to be operated on for peptic ulcer should have a preliminary gastroscopic study, as frequently the symptoms are due to hypertrophic gastritis. In such cases roentgen examination may show only one of the numerous ulcers and erosions that are actually present. This concept is undoubtedly correct. The demonstration of multiple erosions or ulcers or of severe gastritis may be of great importance in deciding on the type of surgical procedure to be

147 Einhorn, M. Quel est le rôle de la gastrite chronique dans l'étiologie de l'ulcère peptique? *Bull. Acad. de med. de Roumanie* **2** 165, 1937.

148 Taylor, H. History, Technique and Clinical Value of Gastroscopy, with Report on Sixty Cases, *Brit. J. Surg.* **24** 469, 1937.

149 Schindler, R., and Giere, N. Gastric Surgery and Gastroscopy. *Arch. Surg.* **35** 712 (Oct.) 1937.

150 Carey, J. B. Gastroscopic Observations of the Postoperative Stomach. *Surg., Gynec. & Obst.* **65** 447, 1937.

adopted or may even show the process to be so extensive that medical treatment should be given further trial. Carey believes that a stomal ulcer is much more readily seen gastroscopically than roentgenographically, although a jejunal ulcer is obviously more readily demonstrated roentgenographically. Carey's article is one of the best of several emphasizing the importance of studies of the preoperative and postoperative condition, and he as well as others points out the excellent opportunity that exists for obtaining direct visual evidence of the efficacy of various forms of therapy.

The problem of gastric ulcer obviously has received the careful attention of numerous observers. As in many aspects of gastroscopic study, little that is absolutely new has been added, but much interesting material has been accumulated. Schloss, Ettinger and Pratt¹⁴³ observed a gastric ulcer in 18 cases, in only 11 of which it was visible roentgenographically. These were true peptic ulcers and not superficial erosions. This has been noted by other observers, but it should also be noted that the converse is true and that both methods of examination should always be employed. Baumel points out that an old ulcer during a period of quiescence is less red than a new active ulcer and that the periulcerous base of the old ulcer is smaller, showing a tendency to equalization of the colors of the diseased and of the healthy parts of the mucosa. During the evolution of the ulcer toward healing, the defect becomes whiter than the surrounding tissue and lustrous. He, as have others, points out the value of repeated observations in an evaluation of the effect of various forms of therapy. Such a study was made by Frohlich¹⁵¹ during the course of treatment of chronic gastritis with a 4 per cent solution of levohistidine monohydrochloride in an isotonic medium. Repeated gastroscopic study showed progressive improvement in the appearance of the mucosa, with the disappearance of erosions and edematous areas. His series included only 5 cases, however, a group that is too small to warrant any conclusions.

• With regard to gastric cancer, few hold the extreme view of Schindler that malignant lesions can be diagnosed with certainty gastroscopically, although all agree that valuable diagnostic aid can be obtained in this way. Baumel¹⁵⁰ believes that the first suspicious gastroscopic sign of cancer is the rigid state of the wall of the stomach even in the absence of any visible lesion. The second important sign is the leukoplakic appearance. After the tumor has developed the malignant ulcer presents an irregular, jagged outline, with edges that are less perpendicular than those of a benign ulcer and often are covered with grayish black material. The mucosa surrounding a malignant ulcer is paler than

151 Frohlich, E. Gastroskopische Befunde bei chronischer Gastritis nach Larostidin-Kur, *Med Klin* **33** 933, 1937

that surrounding a benign ulcer. Baumel feels that the gastroscopic diagnosis of infiltrating cancer of the antrum and pylorus is possible before there are clinical or roentgenographic signs. In such cases the mucosal folds entirely disappear, and the area affected is boardlike and immobile, without any evidence of peristalsis. He recognizes, as do others, the difficulty of differentiating hypertrophic gastritis from pseudopolypomatous or polypoid tumor. Malignant polyps are found to bleed more easily than benign polyps, at the least contact with the gastroscope. Kark¹⁵² reports a case of aplastic anemia with secondary carcinoma following atrophic gastritis in which autopsy showed the stomach to be lined with "thin smooth mucosa devoid of rugae or relief of any sort," except in the pyloric antrum, where there was a small fungating adenocarcinoma. He estimated that the growth was probably of only a few weeks' duration but that the gastritis was clearly of several years' duration. It is pertinent to call attention to such cases in order to emphasize the probable importance of atrophic gastritis in its relation to malignant disease. It is probably a fact that gastric neoplasia arises more frequently from an atrophic mucosa than from an apparently normal one.

Benedict,¹⁵³ in reviewing the results of 456 gastroscopic examinations, again calls attention to the fact that in the so-called atrophic gastritis of pernicious anemia liver therapy rapidly improves the condition of the gastric mucosa. Chevallier and Moutier¹⁵⁴ have also studied the gastroscopic aspect of repair in atrophic gastritis in the anemias, with particular reference to hypochromic and pernicious anemia. They have confirmed the original observations of Jones, Benedict and Hampton in regard to pernicious anemia and, in addition, in regard to the changes in the appearance of the mucous membrane, they comment on the diminished fragility of the mucosa and the apparent diminution in the secretion of mucus after specific treatment. These observers have noted an improvement in the gastric mucosa within three weeks after the initiation of liver therapy, with apparent complete restoration to normal of certain areas in three months. The formation of new areas of mucosa is indicated by the appearance of tiny ruby-colored points which can be readily observed. With regard to the

152 Kark, R. M. Two Cases of Aplastic Anaemia, One with Secondary Haemochromatosis Following Two Hundred and Ninety Transfusions in Nine Years, the Other with Secondary Carcinoma of the Stomach, *Guy's Hosp Rep* **87** 343, 1937.

153 Benedict, E. B. The Importance of GastroscoPy in Surgical Diagnosis, *Am J Surg* **40** 5, 1938.

154 Chevallier, P., and Moutier, F. Aspect gastroscopique de la réparation des gastrites atrophiques dans les anémies et les méthanémies, *Arch d mal de l'app digestif* **27** 437, 1937.

atrophy of the gastric mucosa in pernicious anemia, it should be pointed out that it is entirely probable that the process is not true atrophic gastritis but rather an atrophic process secondary to what is generally accepted as a deficiency disease

The difficulty of differentiation between acute gastritis and perforated peptic ulcer is discussed by Klostermeyer¹⁵⁵ He points out that such severe forms of gastritis are found more frequently in patients with long-standing gastric complaints due to gastritis He reports the findings in 80 such cases in which operation was performed because of the impossibility of making a diagnosis At operation no perforation was seen but there was acute gastritis, with fresh inflammatory erosions in the resected specimens Five such cases occurred in the author's experience in one year in the Hamburg Clinic One is somewhat inclined to wonder at the necessity for gastrectomy in such instances, but it cannot be denied that the observations are of clinical interest

One case reported by Touraine, Moutier and Soulignac¹⁵⁶ is of interest because of a rare finding The 70 year old patient had typical cutaneous lesions of mycosis fungoides, with atrophic gastritis, splenomegaly and marked eosinophilia Gastric lesions are rare in mycosis fungoides, when they occur they usually take the form of mucosal tumors resembling tumors of the skin This is the first report of gastric atrophy in this disease, but it must be admitted that the findings may have been only coincidental

THE SMALL INTESTINE

Interest in the clinical and physiologic aspects of disturbances of the small intestine has increased greatly in recent years With the addition of newer methods for making physiologic studies, real contributions are constantly being added to the knowledge of this rather blind portion of the digestive tract

An ingenious attempt has been made by Irving, McSwiney and Suffolk¹⁵⁷ to isolate functionally the afferent fibers from the stomach and small intestine Dilatation of the pupils of the cat anesthetized with chloralose (a compound of chloral hydrate and dextrose) and reflex changes in the blood pressure in a similar preparation were utilized as indexes of visceral afferent stimulation The gastric and duodenal

155 Klostermeyer, W Die akute Gastritis unter den Erscheinungen einer Ulkus-Perforation, München med Wchnschr **84** 695, 1937

156 Touraine, A Moutier, F, and Soulignac Mycosis fongoïde avec gastrite atrophique, splénomégalie et forte éosinophilie sanguine, Bull Soc franç de dermat et syph **44** 417, 1937

157 Irving, J T, McSwiney, B A, and Suffolk, S F Afferent Fibers from Stomach and Small Intestine, J Physiol **89** 407, 1937

mesenteries are innervated by the vagus and splanchnic nerves and are sensitive to traction. The jejunal mesentery seems to be supplied by the splanchnic nerves. The body of the stomach, pyloric antrum and sphincter were sensitive to distention and were innervated with afferent fibers to the vagus and sympathetic nerves. The lowest threshold to distention was obtained from the pyloric sphincter. The right and left splanchnic nerves supply afferent fibers to the stomach and duodenum. The jejunum and ileum are much less sensitive to distention than are the stomach and duodenum. The right and left splanchnic nerves appear to be the main afferent pathway from these regions.

The effect of vitamin A deficiency on the gastrointestinal tract was studied in monkeys by Verder and Petran¹⁵⁸. The gross structural changes resulting from vitamin A deficiency were hyperplasia of the mesenteric lymph nodes and hyperemia of the intestinal mucosa. These were definite in the small bowel but not striking in the colon.

Yoder¹⁵⁹ found evidence in rachitic rats that vitamin D in optimal amounts increases intestinal motility by about 25 per cent. By inference one draws the conclusion that in vitamin D deficiency, motility is distinctly reduced. The same author¹⁶⁰ also studied the effect of vitamin D therapy on intestinal reduction of iron. Previous experiments on rachitic rats had shown that iron passes through the digestive tract in these animals in a less reduced state. Intestinal reduction of iron rose from a low value for the ileum to relatively high values for the cecum and colon in rachitic rats. Vitamin D therapy had little effect on the reduction of iron in the ileum but brought about a definitely decreased reduction in the cecum, colon and feces.

Beazell, Schmidt and Ivy¹⁶¹ have carried out experiments on the effect of heat on the flow of blood and lymph in the intestinal tract. Heat was applied to the lumen of isolated segments of the small intestine and colon, with temperatures ranging from 52.2 to 57.7 C. It was shown that the flow of blood locally was markedly increased, even to the extent of being quadrupled, without effect on the rate of flow of lacteal lymph. Coincident with the increase in blood flow was an increase in the secretion of succus entericus. As long as there was no interference with the blood supply of the bowel by overdistention or contraction, the viscus might be heated to 52.2 C. Temperatures over

158 Verder, E., and Petran, E. Vitamin A Deficiency in Rhesus Monkey. Studies on Gastro-Intestinal Tract, Blood and Nervous Symptoms, *J Infect Dis* **60** 193, 1937.

159 Yoder, L. Effect of Vitamin D on Intestinal Atony of Rickets, *Am J Digest Dis & Nutrition* **3** 828, 1938.

160 Yoder, L. Effect of Vitamin D on Intestinal Iron Reduction, *Am J Digest Dis & Nutrition* **3** 829, 1937.

161 Beazell, J. M., Schmidt, C. R., and Ivy, A. C. Effect of Heat on Blood and Lymph Flow from Gastro-Intestinal Tract, *Am J Physiol* **119** 197, 1937.

this, however, were found to be dangerous, the injury resulting in a diminished flow of blood and an increased flow of lymph

Studies by Robertson¹⁶² on intestinal stasis due to a low intake of minerals showed that in children, diets low in calcium and potassium are constipating and may cause stasis in the appendix. When given a barium sulfate meal, 6 of 18 children with diets low in calcium and phosphorus retained the barium in the appendix for from four to twenty-one days. These same children when receiving normal diets showed no barium in the appendix for more than one day.

Alvarez¹⁶³ describes a simple apparatus for the study of intestinal peristalsis. By means of this apparatus it is possible to squirt with measured force a measured amount of fluid into the duodenum. In normal rabbits such stimulation usually produced a peristaltic rush. This was studied by a new enterograph, which was devised to record distention of the bowel and the passage of fluid into the lumen. A detailed description of these studies is given.

Alvarez¹⁶⁴ also made studies on intestinal peristalsis in rabbits to determine the effects of nicotine. The drug tended to cut down intestinal peristalsis, and there seemed to be a gradient of susceptibility in the small bowel, the oral end being more susceptible. Most susceptible of all structures seemed to be certain synapses in Auerbach's plexus and the ganglion cells. The effects of the drug wore off quickly.

Roentgenologic studies on the gastrointestinal rate were performed by Wallace and his associates¹⁶⁵ on 52 ambulatory patients, none of whom had any disease that might affect gastrointestinal motility. The rate of progress of a barium sulfate meal was followed by observations at six hours and every twenty-four hours thereafter until evacuation was complete. Less than 10 per cent of the patients evacuated the barium in twenty-four hours, two thirds required three days and the remainder did not completely expel the barium meal until the fourth or the fifth day. This observation that the normal gastrointestinal tract may require as long as one hundred and twenty hours to expel a barium meal agrees with experimental results but represents a longer period than has formerly been obtained by a similar method of examination. Such a conception of normal gastrointestinal motility, of course, has been demonstrated by Alvarez, Hurst and others, but in view of the

162 Robertson, E. C. Intestinal Stasis Due to Low Mineral Intake, *Am J Dis Child* 53:500 (Feb.) 1937.

163 Alvarez, W. C. Peristaltic Rush Studied with New Apparatus, *Am J Digest Dis & Nutrition* 4:225, 1937.

164 Alvarez, W. C. Effect of Nicotine on Intestinal Peristalsis, *Am J Digest Dis & Nutrition* 4:417, 1937.

165 Wallace, R. P., Ehrenfeld, I., Cowett, M., Jolliffe, N., Shapiro, B., and Sturtevant, M. Motility of the Gastro-Intestinal Tract, *Am J Roentgenol* 39:64, 1938.

constant attempts of many pharmaceutic houses to push the sales of drugs to promote "proper evacuation," such evidence is refreshing and timely

An excellent article on the action of morphine on the digestive tract is presented by Krueger¹⁶⁶ In it he reviews the important experimental work since the original observations of Magnus (1908) The effects of the drug in causing gastric slowing and an increase in tone of the pyloric sphincter, augmented propulsion in the small intestine and digestive secretory changes, together with the mechanism of constipation secondary to the use of morphine, are all thoroughly covered in this article The factors contributing to the constipating effect of the drug may include any or all of the following decreased digestion due to diminution in biliary and pancreatic secretion, decreased propulsive activity, increased viscosity of the intestinal contents due to greater absorption of water and closure of the pyloric sphincter Many of the points are hypothetic, but the article is intensely interesting

Miller¹⁶⁷ has reviewed his important studies of the function of the small bowel by means of intubation experiments He discusses in detail the factors involved in the maintenance of physiologic conditions in the small bowel Under varying conditions the small intestine tends to maintain a reaction and an osmotic pressure similar to those of the blood plasma The control of gastric evacuation is an important factor The alkaline fluids of the duodenum are primarily involved in the neutralization of gastric acid When the osmotic pressure of the acid chyme is high, reduction takes place partly by a process of dilution in the stomach and duodenum and partly by absorption in the duodenum Miller attempts to correlate certain clinical observations on the basis of his experimental findings For example, he believes that he can explain the fact that drinking water when the stomach is empty often leads to prompt evacuation of the bowel, the fact that the oral administration of hydrochloric acid in some cases of achlorhydria slows up gastric evacuation and controls gastrogenous diarrhea, the fact that in some instances a dilute solution of sodium bicarbonate taken when the stomach is empty gives a loose bowel movement, whereas a stronger solution may have no effect, and the fact that a small amount of highly concentrated sweet food may give a sense of distention because of the filling of the stomach with its own secretion in an attempt to dilute the hypertonic solution

166 Krueger, H Action of Morphine on Digestive Tract, *Physiol Rev* **17** 618, 1937

167 Miller, T G Intubation Studies of the Human Small Intestine IX Factors in the Maintenance of Physiologic Conditions, *Rev Gastroenterol* **4** 115, 1937

Abbott, Karr and Miller¹⁶⁸ discuss the factors concerned in the absorption of dextrose from the jejunum and ileum, with particular reference to the ability of the small intestine to maintain isotonicity of its contents. The propulsive activity of the small intestine appears to increase as the concentration of dextrose rises above 5.4 per cent. Using a solution containing dextrose in the concentration naturally occurring in the jejunum and ileum (5 per cent and under), the authors found that the rate of absorption varied directly with the concentration.

Groen,¹⁶⁹ using a modification of the method of Miller and Abbott, studied the intestinal absorption of dextrose, galactose and levulose. He showed that a given length of the human small intestine during a constant interval absorbs a constant amount of simple sugar from a concentrated solution. The amount of sugar absorbed increases with an increase in intestinal surface and is proportional to the time allowed for absorption. The addition of dilute acid or alkali to the dextrose solution diminishes the amount of sugar absorbed. No influence of the immediately preceding diet or of starvation on the rate of absorption could be detected. A possible criticism of Groen's studies lies in the fact that he closed off only the lower part of the intestine and that therefore it was impossible for him to measure with absolute accuracy the area of absorbing surface involved in any given experiment.

Further studies by Groen¹⁷⁰ involved the absorption of dextrose from the small intestine in deficiency diseases. Using the same method as in the preceding experiments, he found a diminished absorption of dextrose in 3 patients with diarrhea associated with organic disease of the intestine and in 10 patients suffering from dietary deficiency, such as pernicious anemia and pellagra. In 2 cases of scurvy the absorption of dextrose appeared to be normal. Four of the patients with deficiency diseases were treated by means of an adequate diet, and after successful therapy normal absorption of dextrose was found. Groen feels that the diminished absorption in these cases was not due to increased motility but rather was the result of a defect in intestinal absorption.

Verzar,¹⁷¹ in some interesting experiments on rats, apparently has shown that adrenalectomy is associated with definite changes in intestinal absorption. In adrenalectomized animals, dextrose seemed to be absorbed at the same rate as xylose, similar effects were noted on the

168 Abbott, W. O., Karr, W. G., and Miller, T. G. Intubation Studies of the Human Small Intestine. VII. Factors Concerned in Absorption of Glucose from Jejunum and Ileum, *Am J Digest Dis & Nutrition* 4:742, 1938.

169 Groen, J. The Absorption of Hexoses from the Upper Part of the Small Intestine in Man, *J Clin Investigation* 16:245, 1937.

170 Groen, J. The Absorption of Glucose from the Small Intestine in Deficiency Disease, *New England J Med* 218:247, 1938.

171 Verzar, F. Adrenal Cortex and Intestinal Absorption, *Am J Digest Dis & Nutrition* 4:545, 1937.

absorption of fat The administration of adrenal cortex extract restored the rate of absorption of dextrose to a level four times that of the absorption of xylose and increased the absorption of fat Furthermore, the author believes that under the experimental conditions lactoflavine is not phosphorylated, a synthesis which probably takes place in the intestinal mucosa under normal conditions

Sinclair and Smith¹⁷² discuss the theory of phospholipid changes in the intestinal mucosa This turnover of phospholipids within the mucous membrane lining the small intestine may be due to (1) active combustion of phospholipid within the epithelial cells, (2) continued synthesis and carriage of phospholipid into the blood stream or (3) involvement of phospholipid as an intermediary product in the resynthesis of neutral fat From the results of their studies the authors suggest that in the enzymic synthesis of phospholipid in the intestinal mucosa there is a selection of one molecule of saturated fatty acid for each molecule of unsaturated fatty acid

The influence of fat on the absorption of dextrose from the alimentary canal was studied by Wishnofsky, Kane and Spitz¹⁷³ in a series of 11 diabetic patients Their findings seem to indicate that, contrary to the usual opinion, the rate of absorption of dextrose mixed with fat is not appreciably less than that of dextrose alone

Doubilet and Reimer¹⁷⁴ were able to study the absorption of fat from the ileum in a patient with a temporary Thiery fistula They observed that the fluid secreted from the midportion of the ileum contained about 2 per cent lipoids Olive oil and oleic acid were absorbed, even in the absence of bile acids, which in small amounts apparently had little or no effect on the rate of fat absorption The administration of deoxycholic acid in large amounts increased the volume of fat excreted and subsequently tended to reduce the rate of its absorption

Johnson¹⁷⁵ was able to separate and study colonic and ileal excretion in 3 patients with tumor of the cecum which necessitated both ileostomy and colostomy In 2 of the 3 patients the content of the terminal portion of the ileum was acid at all times, and in the third patient it was usually acid After an increase in peristaltic rate, however, the content became approximately neutral As was to be expected, after the ingestion of a large amount of water the ileal content became more fluid.

172 Sinclair, R G, and Smith, C Turnover of Phospholipids in Intestinal Mucosa, *J Biol Chem* **121** 361, 1937

173 Wishnofsky, M, Kane, A P, and Spitz, W C Influence of Fat on Absorption of Dextrose from Human Alimentary Canal, *Am J Digest Dis & Nutrition* **4** 174, 1937

174 Doubilet, H, and Reimer, M Absorption of Fat from the Ileum in Human Beings, *Arch Int Med* **59** 857 (May) 1937

175 Johnson, R M Absorption and Excretion of Calcium and Phosphorus in Three Patients with Colostomy and Ileostomy, *J Clin Investigation* **16** 223, 1937

with an associated increase in weight of the wet, dry and mineral excretion. Diuresis was associated with a concentration of the ileal excreta, and the more concentrated content contained more calcium and phosphorus per gram of dry weight than did the hydrated content. No evidence was obtained that cholesterol had any specific effect on the absorption of calcium from the intestine in these cases. In the 3 patients the colon failed to excrete significant amounts of calcium and phosphorus at any time.

The absorption of iron from the intestine was found by Heath and his collaborators¹⁷⁶ to be inhibited when it was administered in small doses with relatively large amounts of mucin to patients with hypochromic anemia. These authors infer that increased amounts of mucus in the gastric contents in the presence of achlorhydria may play some role in the malabsorption of iron, especially when the diet is deficient in this substance.

Immediate and late effects of total colectomy or colonic exclusion with ileostomy were studied in 45 cases by Whittaker and Barger¹⁷⁷. It was found that the values for calcium in the serum were reduced after operation but returned to normal within one month. There were no other apparent disturbances in the equilibrium of the chemical constituents of the blood. As has been previously noted, definite dilatation of the terminal portion of the ileum was the usual result. The authors observed that the initial watery ileal discharge gradually thickened during the first three months, and they felt that this concentration of the ileal discharge was unrelated to the time necessary for ingested food to be expelled through the ileac stoma. They concluded that there was no fundamental change in motor activity or in intestinal response to ingested food throughout the prolonged period following operation and believe that no permanent metabolic deficiency followed ileostomy. They fail to emphasize, however, the immediate depletion that is so frequently seen in an aggravated form during the first weeks of the postoperative period following ileostomy. This depletion may be associated with various manifestations of deficiency disease and has been noted by numerous writers.

Welch, Masson and Wakefield¹⁷⁸ indicate one of the factors that may be operative in bringing about depletion during the postoperative

176 Heath, C M, Minot, G R, Pohle, F S, and Alstead, G. Influence of Mucin upon Absorption of Iron in Hypochromic Anemia, *Am J M Sc* **195** 281, 1938.

177 Whittaker, L D, and Barger, J A. Observations on Human Being Following Colectomy or Colonic Exclusion with Ileostomy, *Surg, Gynec & Obst* **64** 849, 1937.

178 Welch, C S, Masson, J C, and Wakefield, E G. Clinical and Laboratory Findings After Excessive Loss of Intestinal Fluid from the Ileum, *Surg, Gynec & Obst* **64** 617, 1937.

period These authors noted that there was an excessive loss of salt and water through the ileac stoma after ileostomy Normally about 2 per cent of the total output of sodium is eliminated by the gastrointestinal tract and the remainder through the urinary tract In their patient 91 per cent of the sodium in the diet was eliminated by the ileostomy, 9 per cent being recovered in the urine Twenty-seven per cent of the estimated intake of chloride was eliminated by the ileostomy, although under ordinary conditions about 2 per cent is lost by way of the intestinal tract

Intestinal obstruction is still a fertile field for investigation, both from the theoretic and from the practical point of view Aird,¹⁷⁹ from a series of experiments on intestinal obstruction, concludes that the diminution in the volume of effective circulating blood from the loss of blood and plasma through the intestinal wall is a trivial factor in simple low intestinal occlusion and is not severe enough to cause death in cases of obstruction due to a closed loop He thinks that it is an important feature of venous strangulation of the bowel and states that in a case of strangulation of a long loop, more than one third of the blood volume may be lost into the dilated intestinal vessels, tissue spaces of the intestinal wall and lumen, and into the peritoneal cavity Extensive volvulus and extensive mesenteric vascular occlusion are thus primarily dangerous as forms of internal hemorrhage and are the only types of obstruction in which benefit is likely to result from blood transfusion In cases of strangulation of an intestinal loop of medium length, Aird and Henderson¹⁸⁰ found a high concentration of histamine in the peritoneal transudate This concentration was not high enough to be regarded as the sole lethal factor in fatal cases It is thought that the specific toxins present in the transudate and responsible for death are still unknown

Scudder, Zwemer and Truszkowski¹⁸¹ produced intestinal obstruction in cats at various levels and noted a rise in the potassium content of the blood to levels which have previously been shown to be lethal They suggest that potassium is the dialyzable toxic factor sought for in intestinal obstruction Their findings are corroborated by those of Cutler and Pijoan,¹⁸² who found that in high intestinal obstruction

179 Aird, I Experiments in Intestinal Obstruction Role Played by Diminution of Effective Circulating Blood Volume in Acute Intestinal Obstruction, *Edinburgh M J* 44 28, 1937

180 Aird, I, and Henderson, W K Intestinal Strangulation Histamine Content of Peritoneal Transudate from Strangulated Intestinal Loops, *Brit J Surg* 24 773, 1937

181 Scudder, J, Zwemer, R L, and Truszkowski, R Potassium in Acute Intestinal Obstruction, *Surgery* 1 74 and 486, 1937

182 Cutler, E C, and Pijoan, M Certain Chemical Factors in Experimental High Intestinal Obstruction, *Surg, Gynec & Obst* 64 892, 1937

there is a definite factor of delayed absorption in the duodenum, with an associated increase in the potassium content of the blood. They, too, speculate as to the possible contributory role of a high potassium content as the cause of death in intestinal obstruction.

The concentration of volatile bases in the fluid contents of the intestine after low ileal obstruction in dogs was found by Hibbard and Kremen¹⁸³ to vary from 0.14 to 1.6 per cent. The volatile bases contained ammonia (50 per cent) and primary and tertiary amines. The length of life in cases of ileocecal obstruction was shortened when the animals were fed a meat diet rather than a meatless diet. When the p_H of the intestinal contents obtained from dogs dying of intestinal obstruction was raised to the antemortem level and placed in the intestinal loops of normal animals, toxic symptoms appeared and were followed by death. The distillate containing volatile bases was found to possess the same characteristics, but the base-free residue was entirely innocuous. The authors conclude that if volatile bases are present in sufficient concentration at an optimal p_H and if they are absorbed in cases of intestinal obstruction, severe toxic symptoms occur, with a fatal outcome.

An interesting clinical observation has been made by Estes,¹⁸⁴ who examined the obstructed loop in 4 cases after anastomosis for intestinal obstruction due to adhesions. In these cases diarrhea, pain, increased peristalsis and at times vomiting followed the first operation and led to resection of the sidetracked loop. Examination of the resected material revealed apparent stasis, some persistence of obstruction or constriction of the intestine, enteritis and ulceration. These findings were reproduced experimentally in dogs when anastomosis was made around an obstruction.

In an excellent review of his previous observations, Wangensteen¹⁸⁵ summarizes the hazards of intestinal obstruction and outlines in detail the rationale of treatment in this condition. Fine¹⁸⁶ also reviews his previous work and gives his further experience in the use of 95 per cent oxygen in deflating the distended bowel when other known nonoperative measures fail. Fine feels that the method is valuable in the treatment of distention, either of functional or of mechanical origin, and that it may be used to advantage before or after enterostomy for obstruction.

183 Hibbard, J. S., and Kremen, A. J. Effect of the Volatile Base in Fluid Intestinal Contents on Dogs with Low Intestinal Obstruction, *Surgery* **3** 325, 1938.

184 Estes, W. L., Jr. Enteritis of Obstructed Loop Following Entero-Anastomosis for Intestinal Obstruction, *Ann Surg* **105** 871, 1937.

185 Wangensteen, O. H. Rationalizing Treatment in Acute Intestinal Obstructions, *Surg, Gynec & Obst* **64** 273, 1937.

186 Fine, J., Hermanson, L., and Frehling, S. Further Clinical Experiences with Ninety-Five per Cent Oxygen for the Absorption of Air from the Body Tissues, *Ann Surg* **107** 1, 1938.

Symptoms of oxygen poisoning were avoided by interrupting the administration of the gas every four to eight hours. The length of time necessary to produce a therapeutic effect varied with the individual case, in accordance with the volume of air to be absorbed and the relative extent of the surface available for absorption.

Various clinical aspects of disease of the small bowel are reported but for the most part do not warrant inclusion in this review. Freilich and Coe¹⁸⁷ discuss the clinical picture of jejunal intussusception, which is most commonly seen in adults and which is usually caused by a tumor due to some local cause of obstruction. In children, jejunal intussusception is commonly found with no apparent cause. In 3,784 cases of intussusception, an enteric type occurred in 14 per cent and a jejunal type in only 0.9 per cent of the cases.

Foucar¹⁸⁸ adds a rather complete review of the literature on syphilis of the gastrointestinal tract, in it he includes a description of 12 cases of syphilis of the small intestine and 1 interesting case of gumma of the transverse colon.

Among the many reports on regional ileitis, an article by Jellen¹⁸⁹ may be mentioned, mainly because it contains a good summary of the roentgenologic findings in this ill defined condition.

A good discussion of malignant tumor of the small intestine is presented by Nickerson and Williams¹⁹⁰. The article includes a brief summary of the literature and a presentation of 10 cases in which the tumor was discovered at autopsy over a forty-year period. A corollary is found in an article by Rowe and Neely,¹⁹¹ who discuss malignant growths of the small intestine and review in particular the roentgenologic aspects of the diagnosis of this condition.

An interesting clinical observation on spasmodic intestinal complications in pernicious anemia is presented by Weil and Ménétrier¹⁹². These authors describe the appearance of a pseudotumor, which produces clinical symptoms of pyloric constriction and gives the roentgenographic appearance of amputation of the pylorus. They believe that these mani-

187 Freilich, E. B., and Coe, G. C. Jejunal Intussusception, *Ann Surg* **105** 183, 1937.

188 Foucar, F. H. Syphilis of Gastro-Intestinal Tract. Report of Case of Gumma of Transverse Colon with Review of Literature, *Am J Path* **13** 65, 1937.

189 Jellen, J. Regional Ileitis. Review of Fifty Cases, *Am J Roentgenol* **37** 190, 1937.

190 Nickerson, D. A., and Williams, R. H. Malignant Tumors of the Small Intestine, *Am J Path* **13** 53, 1937.

191 Rowe, E. W., and Neely, J. M. Primary Malignancy of Small Intestine, *Radiology* **28** 325, 1937.

192 Weil, P., and Ménétrier, H. Complications intestinales spasmodiques au cours de l'anémie pernicieuse, *Bull et mem Soc med d hôp de Paris* **53** 145, 1937.

festations are due to muscular spasm and note that they disappear with liver therapy

Experimental studies have been carried out by Chandler¹⁹³ on the nature of immunity to intestinal helminths, the work being done on white rats. The article is chiefly concerned with a discussion of the details involved in parenteral and intestinal immunity. The latter may be a part of the general immunity stimulated by parenteral immunization, although it may be developed independently.

Differences of opinion still exist as to the pathogenesis of infestations with *Lambia*. Irazabal-Luigui,¹⁹⁴ in the belief that these parasites may be the cause of symptoms, sought for an effective specific agent. Tincture of carobine, pyrethrin, gentian violet, acetarsone, naphthalene and essence of turpentine were all used as therapeutic agents. The author concludes that essence of turpentine is of definite value in treating lamblasis, although it is not a specific. The other medications showed no beneficial effects.

THE COLON

In addition to numerous clinical and statistical studies of diseases of the colon, too numerous to be discussed in this review, a number of original contributions have appeared. These may be divided into three main groups: (1) contributions to the physiology of the colon, (2) descriptions of unusual diseases or complications and (3) contributions to the therapy of colonic diseases.

The contributions to the physiology of the colon include those dealing with metabolism, motility, dynamic pathologic anatomy, innervation, pharmacology, allergy and bacteriology. These subjects will be discussed in order.

An outstanding contribution to the knowledge of metabolic changes dependent on ulcerative colitis is made by Welch, Adams and Wakefield¹⁹⁵. They studied 3 cases of idiopathic ulcerative colitis. The patients were given standard diets. The most outstanding metabolic feature was the abnormally high output of nitrogen in the feces. This was accompanied by a low urea nitrogen content of the blood, which varied from 8 to 20 mg per hundred cubic centimeters. However, the excretion of fat in the feces was not in excess of that found for normal persons ingesting similar diets. The authors conclude that the increased fecal output of nitrogen was due to destruction of tissue and to the

193 Chandler, A. C. Studies on Nature of Immunity to Intestinal Helminths VI. General Résumé and Discussion, *Am J Hyg* **26** 309, 1937.

194 Irazabal-Luigui, M. Etudes expérimentales sur le traitement de la lamblase, *Ann de parasitol* **15** 29, 1937.

195 Welch, C. S., Adams, M., and Wakefield, E. G. Metabolic Studies of Ulcerative Colitis, *J Clin Investigation* **16**:161, 1937.

presence of such substances as blood and pus in the feces. They feel that the role of the rapid intestinal rate in preventing the absorption of fat has been greatly overemphasized.

Several studies of the motility of the colon have appeared. Galapeaux, Templeton and Borkon¹⁹⁶ placed tandem balloons in the colon of each of 4 cecostomized dogs and then introduced intraluminally quantities of gallbladder bile equal to the maximal amount of water which could be given without altering the motility of the colon. Usually this was about 20 cc. They found that the introduction of gallbladder bile consistently produced a reduction in the motility of the colon but resulted in defecation. The same quantity of water had no effect. The authors conclude that defecation may normally be accompanied by relaxation of the smooth musculature of the colon rather than by stimulation of it. Borkon and Templeton,¹⁹⁷ however, demonstrated in similar preparations that an enema of 100 to 200 cc of oil retained within the rectum for two hundred minutes was accompanied by increased activity of the musculature in all parts of the colon. Lawson and Templeton¹⁹⁸ had previously shown that increasing the balloon pressure or introducing irritants above the inner sphincter of the anus inhibited the tone and activity in the proximal portion of the colon while stimulating active contractions in the rectal region. White and Jones¹⁹⁹ observed the number of peristaltic contractions in the human rectum through the sigmoidoscope. They found that although the resting rectum showed few or none, there were usually definite contractions after the application within the ampulla of the rectum of an irritant such as hypertonic salt solution or oil of turpentine. The application of the same irritant above the rectosigmoid junction, however, produced little or no peristaltic activity. All these findings are consistent with the hypothesis that the muscular activity incident to defecation is stimulated by the passage of fecal matter, possibly through relaxed circular musculature, into the ampulla of the rectum, where its presence through distention and local irritation produces activity of the musculature of the entire colon.

196 Galapeaux, E. A., Templeton, R. D., and Borkon, E. L. The Influence of Bile on the Motility of the Dog's Colon, *Am J Physiol* **121** 130, 1938.

197 Borkon, E. L., and Templeton, R. D. The Influence of Oil Enemas on Colon Motility in the Dog, *Am J Physiol* **118** 775, 1937.

198 Lawson, H., and Templeton, R. D. Studies in the Motor Activity of the Large Intestine. I Normal Motility in the Dog, Recorded by the Tandem Balloon Method, *Am J Physiol* **96** 667, 1931, II The Influence of Balloon Technique upon Colon Motility, *ibid* **99** 87, 1931.

199 White, B. V., Jr., and Jones, C. M. The Effect of Irritants and of Drugs Affecting the Autonomic Nervous System upon the Mucosa of the Normal Rectum and Rectosigmoid, with Especial Reference to "Mucous Colitis," *New England J Med* **218** 791, 1938.

Conflicting data on the presence of the gastrocolic reflex in the dog have appeared Galapeaux and Templeton²⁰⁰ found that filling the stomach with a mixture of yeast and buttermilk or even inflating it with a balloon resulted in stimulation of colonic activity in the dog Slive and Fogelson,²⁰¹ however, using balloons introduced through fistulas in different parts of the colon, were unable to demonstrate the gastrocolic reflex, although they did demonstrate an appetite or feeding reflex A feeding reflex would hardly account for colonic motility after the inflation of a balloon in the stomach, as reported by the former workers

Barclay and Franklin²⁰² investigated the physiology of the defecation reflex They discovered that if digital compression of the bladder or of the large intestine was performed, particularly if there was passage of feces into the rectum, there resulted a marked reflex contraction of the diaphragm and abdominal muscles These observations suggest that the act of defecation is a purely involuntary affair after the proper stimulus to its initiation has occurred

Hartmann²⁰³ advances the idea that the pathologic anatomy of diverticulosis is dependent on the presence of localized areas of muscular weakness and of spasm He reports an instance in which a surgeon who was operating on an inflamed rectosigmoid junction witnessed a powerful contraction of the intestine, during which the taeniae separated and a row of little diverticula popped out Hence, Hartmann believes that diverticula of the colon are usually pulsion diverticula and that the concept of a state of latent diverticulosis may well be tenable He attributes much importance to the possible role of so-called mucous colitis and of lead colic in conditioning this state

The autonomic innervation and the pharmacology of the colon are best considered together The contributions which deal with the neurologic aspects of colonic physiology are those of Lawson and Holt²⁰⁴ and of Manning, Hall and Banting²⁰⁵ Lawson and Holt studied the effect of surgical decentralization and subsequent removal of the inferior

200 Galapeaux, E A, and Templeton, R D The Influence of Filling the Stomach on Colon Motility, *Am J M Sc* **195** 230, 1938

201 Slive, A, and Fogelson, S J Colon Motility An Experimental Study of the Colon in the Dog, *Am J Digest Dis & Nutrition* **4** 17, 1937

202 Barclay, A E, and Franklin, K J Reflexes from Bladder and Large Intestine, *J Physiol* **90** 478, 1937

203 Hartmann, J Zur funktionellen Pathologie der Divertikulosi des Kolons, *Munchen med Wchnschr* **84** 252, 1937

204 Lawson, H, and Holt, J P The Control of the Large Intestine by the Decentralized Inferior Mesenteric Ganglion, *Am J Physiol* **118** 780, 1937

205 Manning, G W, Hall, G E, and Banting, F G Vagus Stimulation and the Production of Myocardial Damage, *Canad M A J* **37** 314, 1937

mesenteric ganglion in dogs. Observations on the motility of the colon were made by the balloon method. They found that division of the spinal ramus of the inferior mesenteric ganglion resulted in a decreased tone in the anal canal and an increased tone in the middle portion of the colon but was without effect on the height or the rate of intestinal conditions. Subsequent removal of the inferior mesenteric ganglion had no constant effect on muscle tone but greatly increased the height of contractions. Manning, Hall and Banting studied the effect of direct stimulation of the vagus nerve on the myocardium and on the gastrointestinal tract. Hall, Ettinger and Banting²⁰⁶ had previously produced myocardial damage and ulceration in the stomach and duodenum by daily intravenous administration of acetylcholine. In anesthetized animals they failed to obtain these changes by direct vagal stimulation. Manning, Hall and Banting, however, developed a technic for chronically stimulating the vagus nerve of unanesthetized animals and produced lesions similar to those resulting from the intravenous use of acetylcholine. White and Jones,¹⁹⁹ by direct observation through the sigmoidoscope, noted changes, consisting of diffuse injection, secretion of mucus, dilatation of veins and a mild degree of spasm of the rectosigmoid junction after the oral ingestion of acetylbetamethylcholine chloride and after the topical application of physostigmine sulfate and pilocarpine hydrochloride. They did not furnish evidence as to the effect of direct stimulation of the parasympathetic nervous system on these tissues. Starr²⁰⁷ studied the pharmacologic effects of carbaminoylcholine chloride in normal persons and in persons with peripheral vascular disease. He concluded that its cholinergic action on the gastrointestinal tract, as compared with that on the circulatory system, was far greater than that of acetylbetamethylcholine chloride. Bosse²⁰⁸ used the drug therapeutically in 62 cases of postoperative intestinal distention and atony of the bladder. It relieved urinary retention in 75 per cent of the 41 cases in which it was tried and was found effective in 21 cases of postoperative distention. The author feels that carbaminoyl choline chloride was considerably more effective than prostigmine and safer than the pituitary preparations. Myerson, Schube and Ritvo²⁰⁹ observed the

206 Hall, G. E., Ettinger, G. H., and Banting, F. G. An Experimental Production of Coronary Thrombosis and Myocardial Failure, *Canad. M. A. J.* **34**: 9, 1936.

207 Starr, I. Carbaminoylcholine (Doryl or Lentin). Its Action on Normal Persons, in Peripheral Vascular Disease, and in Certain Other Clinical Conditions, *Am. J. M. Sc.* **193**: 393, 1937.

208 Bosse, U. Doryl zur Behandlung der Darm- und Blasenatonie, *Klin. Wchnschr.* **16**: 1356, 1937.

209 Myerson, A., Schube, P. G., and Ritvo, M. Effect of Acetyl-Beta-Methyl-Choline on the Atonic Colon, *Radiology* **28**: 552, 1937.

effect of acetylbetamethylcholine chloride on the atonic colon in certain cases of schizophrenia. They found that a 30 mg dose administered subcutaneously generally produced increased tonus and motility of twenty-four hours' duration. Two papers on drugs which supposedly inhibit the muscular activity of the colon are also of interest. Quigley²¹⁰ demonstrated that methylhomatropine bromide was less effective than atropine sulfate in its effect on gastrointestinal motility. In the unanesthetized dog, doses one and one-half times the necessary dose of atropine sulfate were required to inhibit completely the motility of the stomach. It required doses six times as large as the necessary dose of atropine sulfate to inhibit completely the activity of the colon. Novatropin is alleged to be six tenths as toxic as atropine sulfate. Boyd²¹¹ reports investigations on the properties of benzedrine sulfate which indicated that it possesses a specific direct effect, causing contraction of intestinal and uterine smooth muscle. This activity was also shared by ephedrine hydrochloride but not by epinephrine hydrochloride. Hence any relaxing effect which benzedrine may have through its effect in inhibiting the end organs of the sympathetic nervous system is at least in part offset by a direct antagonistic action on smooth muscle.

A common denominator of innervation of the autonomic nervous system, chemical mediation of nerve impulses, capillary physiology, allergy and, more specifically, wheal formation is histamine. Felix,²¹² inspired by the work of Mellanby and of Koessler and Hanke, who have shown that histamine introduced into the gastrointestinal tract rapidly disappears, studied the effect of a preparation of dried intestinal mucus ("toiantil") on histamine. If injected simultaneously with histamine, torantil was found to be without effect in modifying the action of the histamine. If incubated with histamine at 37 C for twenty-four hours, however, it completely inhibited the action of the latter. The extract of mucus was rendered completely inert by heating to 70 C for thirty minutes and was inert at a p_H of from 2.5 to 5. Because of its latent period, thermolability and optimum p_H , the author concludes that toiantil possesses the qualities characteristic of a true enzyme. Attempts to treat intestinal disorders with this preparation will be discussed in the last paragraphs of the present review.

210 Quigley, J. P. The Relative Effectiveness of Atropine and Novatropin on Gastric and Colonic Motility of the Unanesthetized Dog, *J. Pharmacol. & Exper. Therap.* **61** 30, 1937.

211 Boyd, E. M. The Effect of Benzedrine Sulphate on the Bowel and Uterus, *Am. J. M. Sc.* **195** 445, 1938.

212 Felix, J. Experimental and Clinical Investigations of the Action of Histaminase Contained in Extracts of the Mucous Membrane of the Intestines on Histamine, *Acta med. Scandinav.* **95** 1, 1938.

In the field of allergy, Gray and Waltzer²¹³ inoculated into the mucosal wall of the rectum serum from a patient known to be sensitive to peanut oil. When peanut meal was subsequently fed by mouth the sites of passive transfer into which the oil had been inoculated could be seen to swell up and become edematous, gradually to become deep red, to become covered with mucus and finally, in the course of an hour or so, to fade away. The changes commenced six to thirty minutes after the ingestion of the peanut oil. The authors concluded that the changes were due to hematogenous transmission of the antigen. From their description the changes must have resembled closely those observed by White and Jones after the topical application of cholinergic drugs.

Contributions to the bacteriology of several diseases of the colon have appeared. Goodpasture²¹⁴ studied a patient with typhoid at autopsy, one and one-half hours after death. He observed within the plasma cells small gram-negative bacilli, which he assumed to be *Escherichia typhi*. They were present in intestinal lesions and also in regional lymph nodes. He advances the hypothesis that the young plasma cell is an essential cellular host in the typical disease in human beings and serves as a protecting and nourishing medium through the period of incubation and throughout the active course of the disease.

Castellani²¹⁵ describes a rare and little known form of chronic colitis, which he termed *métadysenterie chronique*. He says that the disease is due to a group of organisms for which Cerruti coined the generic name *Castellanus*. Like true dysentery organisms, these organisms do not produce gas on any sugar, but they ferment lactose, with the formation of acid, and slowly coagulate milk. Some strains are motile and others nonmotile. One of the strains is considered to be identical with Sonne's bacillus. The disease is widely distributed in the tropics and subtropics and all over Europe and is characterized by recurrent attacks of simple diarrhea, often interspersed with long remissions. There is no pus or blood in the feces, and the clinical picture often closely resembles that of mucous colitis. A detailed classification of the various strains of organisms, with their characteristic fermentation reactions, is given. Mones and Sanjuan²¹⁶ report on the etiology of ulcera-

213 Gray, I, and Waltzer, M. Studies in Mucous Membrane Sensitivity. III. The Allergic Reaction of the Passively Sensitized Rectal Mucous Membrane, *Am J Digest Dis & Nutrition* 5 707, 1938.

214 Goodpasture, E. W. Concerning the Pathogenesis of Typhoid Fever, *Am J Path* 13 175, 1937.

215 Castellani, A. Un type peu connu de colite chronique, *Presse méd* 45 1823, 1937.

216 Mones, F. G., and Sanjuan, P. D. Colitis ulcerosas graves no amibianas: etiología, diagnostica y tratamiento medico, abstracted by J. A. Bargen and A. E. Mendes Ferreira, *Am J Digest Dis & Nutrition* 4 247, 1937.

tive colitis, advancing the thesis, supported by some evidence, that the disease is caused by a filtrable virus. They were able to find the gram-positive diplostreptococcus of Barger with about equal frequency in a series of 25 cases of idiopathic ulcerative colitis and in a control group of similar size. They were relatively unsuccessful in producing experimental lesions with this organism. They prepared a filtrable virus from ulcers of patients with ulcerative colitis and succeeded in producing ulcerative lesions of the gastrointestinal tract in animals after the intravenous injection of this virus. They found that the virus lost virulence if cultivated on solid medium but retained it if grown on Rosenow's medium. They feel that the virus grew anaerobically at the expense of living streptococci. Fifty-five per cent of all the rabbits which were given injections became ill, while 88 per cent of the rabbits which were given injections of the virus grown on Rosenow's medium became ill. In almost all of them diarrhea developed, sometimes with bloody stools. The digestive tracts showed lesions varying from congestion to deep ulceration. The experimental disease in dogs was more like the disease in human beings than like that in rabbits. More than 80 per cent of the dogs that were given injections became ill. The authors offer no specific therapeutic suggestions.

Paulson and Andrews²¹⁷ report, after an extensive study of the value of complement fixation tests for amebic infestation, that positive results were obtained for 66.7 per cent of the patients with known amebiasis. A number of positive results were also reported for persons with no clinical or other laboratory evidence of infestation. The tests were made on 150 persons, and the samples of blood were sent to three different laboratories in Baltimore. Craig, Sherwood and Arnold antigens were used. Some of the serums were tested with more than one of the antigens, and the incidence of positive reactions varied considerably. The gross number of positive reactions for persons with known amebiasis (66.7 per cent) was lower than the figures published by the aforementioned authors or by Tsuchiya. Paulson and Andrews conclude that the test as performed routinely in the clinical laboratory can be considered as a diagnostic aid but that primary importance should not be attached to it.

Bauknecht,²¹⁸ in studying the effect of indol and its derivatives on the inhibition of the growth of bacteria, found that indol, skatol, indol acetate and indol propionate had an effect in inhibiting the growth of

217 Paulson, M., and Andrews, J. A Comparative Evaluation in Clinical Practice. Complement Fixation in Amebiasis, *Arch Int Med* 61:562 (April) 1938.

218 Bauknecht, H. Die entwicklungshemmende Wirkung von Indol auf Bakterien, *Zentralbl f Bakt* 140:101, 1937.

bacteria far in excess of that of phenol. The concentrations of indol and of phenol required to inhibit the growth of various organisms were as follows:

Organism	Indole	Phenol
Lactic acid bacilli	1 2,000	1 250
Bacillus coli	1 2,000	1 500
Bacillus proteus	1 2,000	1 250
Streptococcus haemolyticus	1 2,000	1 500
Staphylococcus aureus	1 4,000	1 250

In view of such findings one is led to speculate whether the deleterious effects that are usually ascribed to indol and its derivatives may not be counterbalanced by beneficial inhibitory effects on bacterial growth in the bowel.

The descriptions of unusual diseases or of unusual complications of diseases of the colon include a large number of subjects, which in many instances are only superficially related to one another. Perhaps the most important of these is the widening recognition of the intestinal manifestations of lymphogranuloma venereum. Chapman and Hayden²¹⁹ report on a series of 30 patients with "lymphogranuloma inguinale" from various parts of New England. Of these 30 patients, 10 showed only local adenitis and genitourinary manifestations, 4 showed chronic gastrointestinal disease without anal stricture and 16 showed anal strictures with or without other manifestations of the disease. Of the 4 showing gastrointestinal disease without anal stricture, 3 had localized proctitis, while the fourth had regional ileitis. The entire series of 30 patients showed a positive reaction to the Frei test. Paulson²²⁰ separated from the general group of patients with idiopathic ulcerative colitis a small number who gave a positive reaction to the Frei test in whom an antigen prepared from the intestinal content was capable of evoking a positive cutaneous reaction. The positive reaction could be produced either in the person from whom the antigen was isolated or in some other person with venereal lymphogranuloma. Paulson feels that he has presented evidence that the syndrome of ulcerative colitis in certain instances can well be a manifestation of venereal lymphogranuloma. Spiesman, Levy and Brotman,²²¹ in a study of 138 patients with

219 Chapman, E. M., and Hayden, E. P. Lymphogranuloma Inguinale, New England J. Med. **217** 45, 1938.

220 Paulson, M. A New Diagnostic Intradermal Reaction with Bowel Antigen Indicating the Presence of the Virus of Venereal Lymphogranuloma in the Intestine and Differentiating the Colitis Associated with That Virus, J. A. M. A. **109** 1880 (Dec. 4) 1937.

221 Spiesman, M. G., Levy, R. C., and Brotman, D. M. Lymphogranuloma Inguinale. Rectal Stricture and Prestricture, Am. J. Digest. Dis. & Nutrition **3** 931, 1937.

rectal stricture in the Cook County Hospital, Chicago, found that 115 gave a positive reaction to the Frei test and that 89 per cent were women with reputedly low moral standards. Haim and Mathewson²²² found 23 cases of venereal lymphogranuloma in 51 cases of benign rectal stricture in San Francisco. They found a high incidence of positive reactions to the Frei test among patients in a marine hospital and a much lower incidence among the patients in the wards of a general hospital.

The presence of colitis localized on the right side of the colon also received a moderate amount of attention. Crohn and Berg²²³ found that about 10 per cent of their patients with idiopathic ulcerative colitis had lesions localized in the right or transverse colon or both but showed little evidence of disease in the rectum or sigmoid flexure. Dudley and Miscall²²⁴ also emphasize the fact that tumors much like those of regional ileitis can be found in various parts of the gastrointestinal tract, including the colon, and Illtyd-James²²⁵ reports a case in which the picture was similar to that in regional ileitis but the lesions were located wholly within the colon. Ralphs²²⁶ reports 3 cases of chronic inflammatory tumor of the gastrointestinal tract in 2 cases in the ileocecal and in 1 case in the pelvirectal region. There is still much confusion in the use of such terms as colitis, regional ileocolitis and inflammatory tumor, and it is not clear from some of the papers whether the tumor was necessarily idiopathic. There is apparently a field where regional ileitis and ulcerative colitis mimic one another, and a sharp demarcation is still further obscured by such diagnostic possibilities as tuberculosis, diverticulitis, syphilis, venereal lymphogranuloma and neoplasm.

A rare form of granuloma which may be mentioned is amebic stenosis. Christopher²²⁷ reports on a case of amebic dysentery in which the inflammatory process progressed to the point where resection of the entire right and the transverse colon was necessary to relieve intestinal obstruction. Christopher found in the literature a report of only 1 previous case of amebic granuloma in which surgical treatment was required, a fatal case reported by Youmans.

222 Haim, A, and Mathewson, C, Jr. The Incidence of Lymphogranuloma Inguinale in San Francisco, *J A M A* **108** 961 (March 20) 1937.

223 Crohn, B B, and Berg, A A. Right-Sided (Regional) Colitis, *J A M A* **110** 32 (Jan 1) 1938.

224 Dudley, G, and Miscall, L. Inflammatory Tumors of the Gastrointestinal Tract, *Ann Surg* **107** 55, 1938.

225 Illtyd-James, T G. Chronic Regional Colitis, *Brit J Surg* **25** 511, 1938.

226 Ralphs, F G. On Chronic Inflammatory Tumors of the Gastrointestinal Tract, *Brit J Surg* **25** 524, 1938.

227 Christopher, F. Stenosis of the Large Bowel Due to Amebiasis, *Surgery* **3** 75, 1938.

A number of congenital anomalies, principally of the right colon, are reported by various workers but hardly warrant comment

Shanks ²²⁸ has made a study of the position and relations of the colon relative to the development of anomalies. He feels that anomalies may be due to alterations in length, rotation, fixation or size and attempts to explain most of the common variations on this basis. Hardly to be explained on this basis were 3 cases of solitary diverticulum of the cecum reported by Bennett-Jones, ²²⁹ who in addition to his own series cites 17 cases previously reported in the literature. In many cases the diverticulum became the site of inflammation and produced symptoms much like those encountered in appendicitis. However, only 1 of the 11 cases reviewed in the literature terminated in perforation. Another rare congenital abnormality is microcolon, of which 2 cases are reported by Ewing and Cooke ²³⁰. Both occurred in 3 day old children who died postoperatively. That congenital microcolon is a rare anomaly is attested by the fact that in a series of 111,451 consecutive autopsies reported from Vienna, congenital narrowing of the colon was encountered in only 2 cases, while in a series of 150,000 consecutive autopsies reported from Leningrad it was encountered in only 9 cases.

Several unusual causes of intestinal obstruction are also described. Eliason and Erb ²³¹ were able to find in the literature only 38 cases of intestinal obstruction during pregnancy which were attributed to enlargement of the uterus. They add reports of 3 patients from the obstetric service of the Hospital of the University of Pennsylvania. They feel that relief can sometimes be obtained by changes in position and enemas but that otherwise laparotomy and cesarean section are indicated. Hepburn ²³² and Cattell ²³³ each report instances of intestinal obstruction resulting from endometrial implants. Cattell divides the types of involvement of the bowel into three groups: (1) involvement of the rectovaginal septum, (2) involvement of the rectum and sigmoid flexure and (3) endometrial involvement of the entire intestinal wall. He cites 2 cases representing each type. In those cases in

228 Shanks, S. C. Congenital Abnormalities of the Colon, *Brit J Radiol* **4** 261, 1937

229 Bennett-Jones, M. J. Primary Solitary Diverticulitis of the Cecum, *Brit J Surg* **25** 66, 1937

230 Ewing, J. B., and Cooke, W. E. Two Cases of Congenital Microcolon, *Brit J Surg* **25** 506, 1938

231 Eliason, E. L., and Erb, W. H. Intestinal Obstruction Complicating Pregnancy, *Surgery* **1** 65, 1937

232 Hepburn, J. J. Endometriosis as a Cause of Acute Intestinal Obstruction, *New England J Med* **217** 6, 1937

233 Cattell, R. B. Endometriosis of the Colon and Rectum with Intestinal Obstruction, *New England J Med* **217** 9, 1937

which the intestinal lesion was discrete, resection of the sigmoid flexure was performed, in the others the bowel was not resected. In all cases extensive pelvic treatment was carried out, and all the patients showed good recovery. Foucar¹⁸⁸ reports 1 case of gumma of the transverse colon. He has collected reports of only 4 cases from the literature, in none of which had a flexure been affected.

Uncommon tumors or combinations of tumors are also reported. Maingot²³⁴ and Pemberton and Waugh²³⁵ each cite instances of the simultaneous development of carcinoma of the stomach and carcinoma of the colon. Wyatt²³⁶ discusses carcinoid or argentaffine tumors and concludes that they are, contrary to general opinion, potentially malignant. He cites 1 case in which there were metastases, but the patient did well after removal of the primary and secondary lesions. Miller and Sweet²³⁷ emphasize the importance of inheritance in the development of multiple polyposis of the colon and also the frequency with which such lesions eventually become malignant.

Two unusual genitourinary complications were also noted. Hepler²³⁸ describes 2 cases of nonobstructive congenital megaloureter, in 1 of which the condition was associated with megacolon. Feldman²³⁹ describes the development of renocolic fistula as a complication of pyelonephritis. In his patient the renal pelvis had perforated through into the large bowel, and the resultant lesion was mistaken for carcinoma of the colon when an enema of barium sulfate was given.

Wilkie,²⁴⁰ in the course of twenty years of practice, has seen 4 patients with benign ulcer of the ascending colon. In these 4 cases the ulcer became manifest through utterly different clinical syndromes. In view of the extreme rarity of the condition they merit listing separately.

CASE 1—A 45 year old man complained of chronic constipation and pain in the right lower quadrant of the abdomen. At operation a mass was present in the ascending colon which looked much like carcinoma. Pathologic study of the

234 Maingot, R. Primary Carcinoma of the Stomach, Sigmoid and Colon Occurring Simultaneously, *Brit M J* **1** 118, 1938.

235 Pemberton, J J, and Waugh, J M. Primary Carcinomas of the Stomach and Sigmoid Flexure Occurring Simultaneously in the Same Individual, *Surgery* **2** 211, 1937.

236 Wyatt, T E. Argentaffine Tumors of the Gastro-Intestinal Tract, *Ann Surg* **107** 260, 1938.

237 Miller, R H, and Sweet, R H. Multiple Polyposis of the Colon, *Ann Surg* **105** 511, 1937.

238 Hepler, A B. Nonobstructive Dilatations of the Upper Urinary Tract in Children, *J A M A* **109** 1602 (Nov 13) 1937.

239 Feldman, M. Renocolic Fistula, *Am J Digest Dis & Nutrition* **4** 110, 1937.

240 Wilkie, D. Simple Ulcer of the Ascending Colon and Its Complications, *Surgery* **1** 655, 1937.

resected lesion revealed a deep ulcer, much like a gastric ulcer, with induration and small cell infiltration but no evidence of cancer

CASE 2—A 64 year old woman complained of chronic constipation and pain in the right lower quadrant of the abdomen. Physical examination revealed a tender mass in that quadrant. Subsequently a nontender necrotic swelling developed in the inguinal region which looked like a hernia but contained gas. It was found to be continuous with an extraperitoneal cavity extending from the kidney to the pelvis. Autopsy showed an ulcer, 5 mm in diameter, which had perforated through the posterior aspect of the ascending colon.

CASE 3—A 56 year old woman complained of chronic constipation and of diarrhea of eight days' duration. Severe pain and tenderness then developed in the right lower quadrant of the abdomen. She died, and autopsy showed generalized peritonitis resultant on the anterior perforation of an ulcer in the ascending colon.

CASE 4—A 49 year old woman complained of distention and of dragging pain in the right lower quadrant of the abdomen of ten years' duration. At operation a fibrosed stellate scar was present in the ascending colon. There was also a duodenal ulcer.

Two unusual conditions simulating acute abdominal conditions are also placed on record. Cullen and Brodel²⁴¹ describe a syndrome characterized by acute tenderness in the lower portion of the abdomen produced by hemorrhage into the sheath of the rectus abdominis muscle. The symptoms usually occurred after exertion or during pregnancy, and Cullen says that on physical examination it was determined that the tenderness was localized to the area of the muscle sheath. Robertson²⁴² emphasizes that in hyperthyroidism it is possible for a state of abdominal distress to develop which simulates an acute abdominal catastrophe. In 1 of the 3 cases cited the patient had been given thyroid by mouth. Severe pain developed in the right lower quadrant of the abdomen and was accompanied by diarrhea and a white blood corpuscle count of 27,000 per cubic millimeter. At operation, by a well known surgeon, a normal appendix was removed.

Ferguson²⁴³ reports 2 cases of carcinoma of the pelvic viscera in which irradiation was followed by distressing rectal symptoms. Cramps, severe tenesmus, bloody diarrhea and, in 1 case, almost complete incon-

241 Cullen, T. S., and Brodel, M. Lesions of the Rectus Abdominis Muscle Simulating an Acute Intraabdominal Condition. I Anatomy of the Rectus Abdominis Muscle, *Bull. Johns Hopkins Hosp.* **61** 295, 1937. Cullen, T. S. II Hemorrhage Into or Beneath the Rectus Muscle Simulating an Acute Abdominal Condition, *ibid.* **61** 317, 1937.

242 Robertson, W. E., Wohl, M. G., and Robertson, H. F. Hyperthyroidism Masked by Symptoms of Acute Abdominal Catastrophe, *J. A. M. A.* **108** 623 (Feb. 20) 1937.

243 Ferguson, L. K. Secondary Effects of Radiation upon the Rectum Following the Treatment of Extrarectal Pelvic Lesions, *Am. J. Digest. Dis. & Nutrition* **4** 712, 1938.

tinence occurred several months after the treatment. Examination revealed extreme tenderness of the rectum, stenosis due to contraction of the entire rectal wall and a pale, ulcerated mucosa. Treatment includes keeping the stools soft if stenosis is marked and colostomy if necessary. This reaction should be distinguished from extension or metastasis of a neoplasm, which it simulates.

The contributions to the therapy of diseases of the colon may best be divided into those which are primarily surgical and those which are primarily medical. Devine²⁴⁴ describes a technic for operating on the isolated colon after the fecal stream has been diverted. By an ingenious method he performs an initial double-barrel proximal colostomy in which the two ostia are widely separated. In this way it is possible completely to protect the isolated colon from fecal contamination and by daily lavage to approach a state of sterility. Devine has found that it is possible to perform the most radical resection in the distal portion of the colon and rectum without the mortality generally associated with operative work in that region. Reestablishment of fecal flow through the colon is easily brought about through the use of an enterotome, which cuts through the walls of the colon directly beneath the double-barreled enterostomy.

Adson,²⁴⁵ in discussing the surgical treatment of Hirschsprung's disease, outlines four operations on the sympathetic system in current use: (1) the Wade operation, consisting of removal of the first and second lumbar sympathetic ganglions on the left, (2) the Judd and Adson operation, consisting of bilateral removal of the second, third and fourth lumbar ganglions and the intervening trunk, (3) the Rankin and Learmouth operation, consisting of resection of the inferior mesenteric nerves and the presacral nerve, and (4) the new Adson operation, consisting of removal of both trunks, the second, third and fourth lumbar ganglions, the superior hypogastric plexus and the presacral nerve. After this last type of operation the only sympathetic fibers remaining intact are those which course down along the inferior mesenteric artery to the lower portion of the colon and anus. Adson reports follow-up studies of 22 patients with Hirschsprung's disease or an atonic colon, 3 having had extensive splanchnic resection and the rest a limited operation. The patients were from 5½ months to 19 years of age, most of them being under 6 years of age. Most of those in whom the disorder was on the left side were greatly helped, those with symptoms on the right side responded distinctly less well. Two patients

244 Devine, H. Operation of a Defunctioned Distal Colon, *Surgery* 3: 165, 1938.

245 Adson, A. W. Hirschsprung's Disease. Indications for and Results Obtained by Sympathectomy, *Surgery* 1: 859, 1937.

died, 1 on the operating table and 1 a day later. Leriche²⁴⁶ outlines the same group of procedures and, in general, agrees that after any one of them the intestinal movements usually become regular and remain regular with or without a laxative. He decided therefore to try a much simpler operation, i.e., unilateral resection of the splanchnic nerve. This he did in 4 cases (2 children and 2 adults), with excellent results.

Another semisurgical procedure is the use of the electrocautery for the treatment of carcinoma of the rectum. Thorlakson and Hay²⁴⁷ in 10 cases of carcinoma of the rectum or rectosigmoid juncture, employed electrocoagulation, they feel that it offers a means of palliative treatment under certain indications: (1) advanced age, (2) marked general debility, (3) tumor of the rectal ampulla located posteriorly and laterally and (4) refusal of radical surgical treatment. They claim good palliative results in certain instances. However, it seems that there is danger of perforation through peritonealized areas of the rectum and of the rectosigmoid juncture, with the development of generalized peritonitis, and in most instances this hazard should contraindicate such a procedure.

Pneumoperitoneum in the treatment of intestinal tuberculosis is reviewed by Salkin²⁴⁸. He claims good results or complete cure in 72 per cent of 76 white patients and in 76 per cent of 17 Negroes, in other words, in 73 per cent of a total of 95 patients so treated. Unfortunately, he does not publish data regarding a control series treated in another manner, however, the figures appear to be strikingly good. He quotes Banyai and others who have previously obtained good results with the method.

Another form of physical treatment which is reported is the use of artificial fever in ulcerative colitis. Ferguson, Fetter and Schnabel²⁴⁹ treated 4 patients with the Kettering hypertherm. In each instance they maintained a temperature of from 104 to 105 F for two and one half hours three times a week. Each patient received from seven to twelve treatments. The authors feel that they obtained good clinical improvement by this method and that the proctoscopic picture showed a corresponding change toward the normal. It seems probable that such results, if obtained consistently, are similar in character to those claimed

246 Leriche, R. De la section des splanchniques dans la mégacolon non compliqué avec or sans dolichocolon, *Presse méd* 45:1851, 1937.

247 Thorlakson, P. H. T., and Hay, A. W. S. Carcinoma of the Rectum and Rectosigmoid, *Canad. M. A. J.* 38:107, 1938.

248 Salkin, D. Pneumoperitoneum in Intestinal Tuberculosis. An Appraisal of Various Therapeutic Procedures, *Am. Rev. Tuberc.* 33:435, 1936.

249 Ferguson, L. K., Fetter, F., and Schnabel, T. G. Artificial Fever in the Treatment of Ulcerative Colitis. A Preliminary Report, *Am. J. Digest. Dis. & Nutrition* 4:487, 1937.

by the enthusiastic supporters of so-called specific serum therapy. Nor must it be forgotten that spontaneous remissions are characteristic of the disease.

The more purely medical forms of treatment vary considerably in their originality. At least four papers have appeared on the use of aluminum compounds. Eyerly and Breuhaus²⁵⁰ advocate strongly the use of aluminum silicate (kaolin) and of aluminum hydroxide in ulcerative colitis, claiming that the action of these substances is twofold: (1) to remove bacteria mechanically and (2) to remove toxins by adsorption. These actions were originally demonstrated for kaolin by Braaffedt, in 1923. Crohn, in 1929, showed that aluminum hydroxide could effectively be used as a substitute for other alkaline substances in the treatment of peptic ulcer. Smith²⁵¹ prepared a mixture of 20 per cent aluminum silicate and 2.5 per cent aluminum hydroxide suspended in water. Fecal suspensions were placed in graduated cylinders at 37 C: (1) alone, (2) with 3 Gm of kaolin and (3) with 3 Gm of the mixture of kaolin and aluminum hydroxide. Bacterial counts which were made at intervals revealed that the mixture of kaolin and aluminum hydroxide was about five times as effective as kaolin alone in adsorbing or in inhibiting the growth of bacteria. Fradkin²⁵² used approximately such a mixture as an enema for the relief of local symptoms in a case of ulcerative colitis. He employed an enema consisting of 20 per cent kaolin (aluminum silicate), 10 per cent liquid petrolatum and 70 per cent aluminum hydroxide gel and introduced 10 ounces (300 cc) three times a week. He feels that the patient received definite relief. Emery,²⁵³ however, advises against the wholesale use of adsorbants, because of the danger of adsorbing vitamins and because he thinks the adsorbants are likely to dry in the colon, a risk which he feels need not be considered in ulcerative colitis. He considers that neither kaolin nor barium sulfate should be used in cases of diverticulitis, because of the danger of perforating the diverticulum. Without adequate supporting data, the question arises as to whether such objections are not rather academic.

The use of apple powder in the treatment of acute diarrhea has received some attention. Manville²⁵⁴ outlines rather extensively the

250 Eyerly, J. B., and Breuhaus, H. C. Treatment of Ulcerative Colitis with Aluminum Hydroxide and Kaolin, *J. A. M. A.* **109**:191 (July 17) 1937.

251 Smith, W. A Comparison Between the Adsorptive Action of Kaolin and Kaolin-Alumina Mixture on Fecal Bacteria, *Lancet* **1**:438, 1937.

252 Fradkin, W. Z. Control of Rectal Bleeding in Convalescent Ulcerative Colitis Patient, *J. Lab. & Clin. Med.* **22**:877, 1937, abstracted *J. A. M. A.* **109**:464 (Aug. 7) 1937.

253 Emery, E. S., Jr. The Pharmacopeia and the Physician, Use of Absorbents in Gastro-Intestinal Diseases, *J. A. M. A.* **108**:202 (Jan. 16) 1937.

254 Manville, I. A. Use of Apple Powder in the Prevention and Cure of Summer Diarrheas, *Arch. Pediat.* **55**:76, 1938.

rationale for the treatment. Apparently he feels that the colloid hygroscopic action of pectin is capable of adsorbing large numbers of bacteria, but he also feels that uronic acid, which apples contain in amounts up to more than 1 per cent, is an important factor. He says that mucus is composed of a protein fraction and a carbohydrate fraction, the latter being glycuronic acid, which can be synthesized from the uronic acid contained in apples. Hence, the failure of mucous secretion associated with vitamin A deficiency may be in part overcome by the feeding of uronic acid. It might be assumed that the overproduction of mucus in acute diarrhea could be prevented in part by similar therapy.

Another form of treatment for diarrhea based on restoring the intestinal mucus is that suggested by Goth²⁵⁵. After the work of Felix, who demonstrated the presence of an enzyme, histaminase, in an extract of dried intestinal mucus ("torantil") Goth attempted the use of the extract in the treatment of intestinal "allergy". He concludes that relief should be afforded by either of the following mechanisms:

1. Prevention of the formation of histamine
 - (a) Removal of allergens
 - (b) Desensitization to allergens
2. Minimization of the histamine effect
 - (a) Accustomization (histamine feeding)
 - (b) Destruction (by extract of dried intestinal mucus)

He feels, of course, that the preparation of dried intestinal mucus acts by destruction of histamine *in situ* through its enzyme activity. The work is published with no statistical data and with no clinical evidence for the statement that the patients were in fact suffering from intestinal allergy. If the finding of histaminase by Felix is correct, then Goth's therapeutic attempts are rational and of great theoretic interest and should be repeated in a more thorough manner.

Reverting to the subject of Hirschsprung's disease, Reeves and Harrison²⁵⁶ report on the effect of the administration of pancreatic extract. Craven, in 1934, introduced the treatment on the theory that extract of pancreatic tissue is a parasympathetic stimulant. She had demonstrated that it has an immediate effect on the intestines of the guinea pig. Reeves and Harrison used the Sharp & Dohme preparation of pancreatic tissue in acid alcohol. They gave doses up to 3 cc daily and show the roentgenograms taken in 3 cases in which there was striking improvement. They say that they obtained striking improvement in 6 of 8 patients who received this treatment.

²⁵⁵ Goth, A. Ueber die Behandlung der Kolitis mit Torantil, *Deutsche med Wchnschr* **64** 338, 1938.

²⁵⁶ Reeves, R. J., and Harrison, E. K. The Treatment of Hypotonic Megacolon by Administration of Pancreatic Tissue Extract, *Radiology* **28** 731, 1937.

Book Reviews

Porphyryne und Porphyrinkrankheiten By A Vannotti, M D, of the University Clinic, Bern Price, 27 marks Pp 286, with 64 illustrations Berlin Julius Springer, 1937

This is an unusually interesting book and deals with a subject which is of considerable clinical interest. It is divided into ten chapters, the first seven are devoted to the porphyrins, their chemical composition, their importance in biology and their relation to pigment and iron metabolism in general. The eighth and ninth chapters deal with the clinical manifestations of porphyria and their treatment. The tenth chapter is concerned with methods and describes how porphyrin may be quantitatively measured in blood, urine and bile.

The monograph as a whole emphasizes the importance of differentiating between normal and abnormal porphyrin metabolism. The author designates the latter porphyria. He discusses the cutaneous, abdominal and nervous manifestations that may be induced by abnormal porphyrin metabolism. In the chapter on treatment he discusses what may be attempted in the light of current knowledge and leaves one with the feeling that much more is now understood about porphyria than was clear a few years ago. While therapeutic methods to combat this disorder are by no means wholly successful, it is possible at least to control porphyrin metabolism to a certain extent, to mobilize the deposit of porphyrin in the bones and to stimulate its excretion through the kidneys in several ways.

At the end of each chapter is a comprehensive bibliography. In glancing through the references one obtains the impression that comparatively little significant work on porphyrin metabolism has been accomplished in this country, the vast majority of the references are either to the German or the English literature. The book as a whole is well and interestingly written. It deserves recognition.

Dextrose Therapy in Everyday Practice By E Martin, Sc D Price, \$3 Pp 451, with 44 illustrations New York Paul B Hoeber, Inc, 1937

This book presents a survey of the clinical and experimental investigations which were reported between 1900 and 1936 concerning the role of dextrose in normal and abnormal physiologic conditions and its use as a therapeutic agent. The material is exceedingly well organized and is clearly and concisely presented in a practical and usable manner. After a short historical introduction the chemistry of dextrose is discussed, followed by an excellent chapter on its "physiologic action." The author then considers dextrose therapy in diseases of the various systems of the body (gastrointestinal and cardiovascular), in metabolic, deficiency, allergic and infectious diseases, in pregnancy, and in surgical conditions. A separate chapter is devoted to each group of disorders, the symptomatology and pathologic physiology are discussed and the rationale for and therapeutic value of the administration of dextrose are indicated. The final chapter deals with the modes of administration of dextrose. An extensive bibliography is appended to each chapter, amounting in all to over two thousand references. Although numerous statements in the book are controversial and at times dextrose therapy appears in the light of a universal panacea, the monograph is exceedingly valuable, summarizing in a practical way the present status of knowledge of the importance of dextrose in bodily economy and in therapy.

Neurology By Roy R Grinker M D Second edition Price, \$8.50 Pp 999, with 406 illustrations Springfield, Ill Charles C Thomas, Publisher, 1937

As a textbook for students this volume should rank high, as the subject matter is arranged to meet the requirements of the students in an understandable way.

In a textbook on neurology, like one on psychiatry, it is a difficult problem to keep up with the times, as no branches of medicine are receiving more attention and more contributions from scientific minds than are neurology and psychiatry. This is true especially in the line of therapy. On perusing the different chapters of this book and noting the many changes necessary since the issue of the first edition, one must conclude that as an up-to-date textbook it can be recommended. The author has reviewed the recent literature rather thoroughly on the subjects which have attracted those who have given the most time to research. The chapter devoted to the extrapyramidal motor system, as evidenced by the number of references at the end of the chapter, is a good example of the attention given that subject within the past few years, which has shown the interpretation of the pathologic picture of the disease through clinical demonstration. The illustrations are well arranged and instructive.

Neuere Ergebnisse auf dem Gebiete der Krebskrankheiten By Prof Dr C Adam and Prof Dr H Auler Price, 12 marks Pp 366, with 66 illustrations Leipzig S Hirzel, 1937

Forty-seven prominent German authors have collaborated in the presentation of this volume on the subject of carcinoma. The purpose of the compilation is an exposition of the more recent concepts and the more advanced studies on cancer. Each of the various phases of carcinoma is considered in a separate article by an author interested in that particular aspect of the problem.

Professor Dietrich, in discussing the relation of trauma to the development of carcinoma, expresses the view that there has been a tendency to stress this unduly. He states that there are several factors that must work together for the production of tumor, namely, (1) disposition, (2) tumor anlage (embryonal) and (3) cell mutation. According to Professor Schultz, the cachexia associated with carcinoma is the result of autointoxication, due either to break-down products or a secretion of the carcinoma cells. The bluish stippling of the red blood cells observed in some cases of cancer is accordingly a manifestation of toxic degeneration.

Professor Frik states that, in contrast to most American surgeons, Germans prefer postoperative rather than preoperative roentgen therapy in the management of carcinoma of the breast. Of interest in this regard is the statement by Professor Buetzur that there is no danger of metastasis as a result of biopsy. Professor Braun sounds a disconsolate note in his excellent summary of the recorded observations on carcinoma of the liver and pancreas. The interesting analysis of 1,301 cases of rectal carcinoma by Professor Bench is especially noteworthy. Whereas the obtaining of a five year cure in 10 per cent of the cases may appear encouraging, his statement that 75 per cent of all physicians coming to the surgeon have inoperable lesions is most discouraging.

Other articles consider carcinoma of the skin, lungs, prostate and other organs and regions. These give, in general, good summaries and reviews, with expressions of the authors' impressions and a consideration of German opinions.

Eksperimentelle studier over occlusionsicterus By Orla Vadsten Pp 288, with 19 figures and an English summary Copenhagen Nyt Nordisk Forlag, Arnold Busck, 1936

This interesting dissertation is based on rat experiments done at the Institute for Hygiene of the University of Copenhagen and contributes substantially to the knowledge of the abnormal physiology of the obstructive jaundice produced by cutting the ductus choledochus between ligatures. The author considers the question as to which is more important in this condition, (1) the disturbance of digestion and absorption that results from the exclusion of bile from the intestine or (2) the disturbance directly produced in the rest of the body by the bile pigments and bile salts circulating in the body fluids. His experiments confirm the suspicion, based on a thorough review of previous work, that the consequences of obstructive jaundice are primarily digestive and absorptive.

When kept on a standard diet, rats with obstructive jaundice showed no signs of avitaminosis D, and the only sign of avitaminosis A was chronic colpokeratosis. Such rats were more resistant than normal rats to toxic doses of vitamin D given by mouth, but not to vitamin D given subcutaneously. They did not gain in weight if vitamin A was added to the food, but they did if vitamin A was given subcutaneously. When rats with obstructive jaundice were kept on a special diet shown to be adequate for normal rats, severe xerophthalmia developed. Of the 337 rats in which obstructive jaundice was produced, 20.5 per cent had "cholemic" hemorrhages, certain data indicate that the bleeding was associated with reduced absorption of vitamin D. Other results and control procedures which cannot be summarized here are described in the detailed English summary. The bibliography shows a thorough knowledge of recent American work.

Pneumatiseringen og de bestaaendelsesagtige forandringer i processus mastoideus ved mellemøresuppuration, en klinisk-roentgenologisk studie. By Kurte Broste, M.D.

This roentgenologic study of pneumatization of the mastoid and of changes observed associated with suppuration of the middle ear was presented by Dr. Broste as a thesis for the degree of Doctor of Medicine at the University of Copenhagen. One hundred and thirty-four patients were examined along with their clinical histories. It was hoped that such an associated examination would correlate diseases of the middle ear with the changes in the mastoid.

His basic hypothesis was that the degree of mastoid pneumatization is dependent on the vitality of the epithelium of the tympanic cavity and, therefore, that the anatomic development of the mastoid is to be considered as a function of the character of the mucous membrane of the middle ear and that diseases in the middle ear and in the mastoid might therefore be expected to show a correlation. He accepts Wittmaack's classification of three chief variants in the mucoperiosteum of the ear—mesoplastic or normal, hyperplastic and fibrinous. His studies, however, did not support the hypothesis that a special variety of mastoid occurs with either the fibrinous or the hyperplastic type. Suppuration of the middle ear with a mesoplastic mucosa may be expected to run a favorable course. But he was not able to determine definitely a special part played by these variants in pneumatization or on the outcome of mastoiditis.

He sought for a definite picture associated with sinus thrombosis or perisinus abscess, but such could not be determined. Distortion of the contour of the lateral sinus he found to be an untrustworthy guide, since the normal sinus does not always show sharply defined walls.

Though he expresses regret that he was unable to establish any relation between the type of pneumatization and any definite tendency toward complications of the various types, his study is of value because of the variety and significance of the individual cases.

Experimentelle Untersuchungen über das Blut und die blutbildenden Organe besonders das lymphatische Gewebe des Kaninchens bei wiederholten Aderlassen. By Helge Sjøvall. Pp. 308, with tables and charts. Lund: Hakan Ohlssons Buchdruckerei, 1936.

This volume represents an original contribution to the hematologic literature and was "primarily intended to clarify the part played by the lymphatic tissue, and especially the secondary nodules, in lymphocyte production." Rabbits made anemic by repeated bleeding were used as test animals. Many data were obtained, not only on hematologic factors but regarding lymphatic structures as well. Results speak against the secondary nodules as main centers of formation of lymphocytes and for the hypothesis of lymphocytic circulation, with movement from the lymphatic tissue through the blood to the body tissues and back again.

While the book seems unduly long for a report of the studies carried out, one must commend the completeness of the data given. Profuse illustration with charts and tables covers all details of the investigation, including the values of

statistical analysis. The thoroughness and accuracy of the observations are immediately evident. The volume, however, will interest a small group only. The practitioner will find in it little or nothing to attract his attention. It is of value primarily to the research pathologist and hematologist.

Der Myokardinfarkt. Erkennung, Behandlung und Verhütung. By Prof. Max Hoehrein, M.D., Chief of Medicine in the University Clinic, Leipzig. Price, 12.50 marks. Pp. 196, with 52 illustrations. Dresden: Theodor Steinkopff, 1937.

This book, representing the first of a series on the circulation, considers myocardial infarction from the standpoint of diagnosis, management and prevention. One is introduced to the important aspects of the anatomy of the coronary system first and then to the problems of physiology and pathologic physiology. In this way the hemodynamics of the coronary system are made a basis for an understanding of the superstructure, the clinical aspects of coronary occlusion. Particularly emphasized in this connection are the analysis of the symptoms, the diagnosis, including electrocardiographic localization, the differential diagnosis and the treatment.

The work represents an excellent short review of those aspects of coronary disease of greatest interest to the practicing physician. Controversial and theoretic considerations are reduced to a minimum, leaving for the reader a clear but brief exposition of the necessary facts. Another important feature of the book is the breadth of the literature included in its preparation. American works are well represented and are incorporated with European views in the problems of pathogenesis and diagnosis.

An extensive bibliography is appended.

Die inneren Erkrankungen im Alter. By Albert Müller-Dehäm, M.D. Price, 24 marks. Pp. 408. Berlin: Julius Springer, 1937.

Without doubt the medical problems of old age will become increasingly important as the average span of life is prolonged. Moreover, old persons prefer to live comfortably and to remain active as long as they can, hence how best to manage effectually the latter years of life is an important medical problem.

This volume is a textbook on disease as it appears in elderly persons. The author points out that elderly persons react differently to illnesses than do younger ones, cancer, diabetes, the anemias, pneumonia, for example, all are likely to develop in older persons, to respond differently to treatment than in younger persons and to require different management. The cost of surgical treatment is greater in the old person than in the young, not only because convalescence after an operation is longer but also because there is less time left for postoperative accomplishment. Hence, when and how to operate on old persons requires a special kind of surgical judgment.

All such matters and many more are discussed in this book. On the whole, it presents an interesting point of view on an interesting phase of medicine. While a textbook of this character is not likely to be widely read, it is a stimulating reference work. It is worth having on the shelves of any medical library.

Normale und pathologische Physiologie der Bewegungsvorgänge im gesamten Verdauungskanal. Vol. 2. By Prof. Dr. Med. Werner Catel. Price, 15 marks. Pp. 298, with 123 illustrations. Leipzig: Georg Thieme, 1937.

This is the second volume of Professor Catel's thorough work on the motility of the digestive tract. The present instalment is in two parts, the first takes up clinical pathology under such heads as the pathology of swallowing, esophageal spasms and dilatations, pyloric spasms, dilatation of the stomach and so on down the digestive tract. The last section is on pharmacology and deals with the influence of the various common drugs in this domain. The book is handsomely printed, with many excellent illustrations and diagrams as well as an extensive bibliography.

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CHANGES IN THE LIVER PRODUCED BY CHRONIC PASSIVE CONGESTION

WITH SPECIAL REFERENCE TO THE PROBLEM OF CARDIAC CIRRHOSIS

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In cases of congestive heart failure, varying degrees of passive congestion of the liver universally occur from the resulting stasis in the portal circulation. Chronic passive congestion of the liver becomes evident when heart failure becomes protracted or frequently recurrent. At times the liver increases enormously in size, so that it reaches the level of the umbilicus or even lower. Not infrequently the degree of portal stasis is disproportionate to the stasis in the systemic circulation, probably owing to the fact that a greater degree of obstruction to the blood flow from the hepatic veins occurs than to that in the inferior vena cava. Likewise, the capillaries of the portal system are possessed of a relatively high degree of permeability.

The effects of chronic passive congestion on the liver have been the subject of much controversy for nearly a century, the issue involved chiefly concerning the production of hepatic cirrhosis. Becquerel,¹ in 1840, was the first to express the opinion that chronic passive congestion resulting from cardiac failure produces hepatic cirrhosis. The influence of his work was quite far reaching and fostered adoption of the term *cirrhose cardiaque*. This belief received the support of Rokitsky²

From the Section on Cardiology, the Mayo Clinic

This investigation was made while Dr. Boland was Fellow in Medicine at the Mayo Foundation, Rochester, Minn.

The pathologic investigation in this study was made by Dr. Boland under the direction of Dr. H. E. Robertson, of the Section on Pathologic Anatomy, the Mayo Foundation, in partial fulfillment of the requirements for the degree of Master of Science in Medicine. Clinical correlations and the discussion, together with reorganization of the material, are the work of Dr. Willius.

1 Becquerel, A. *Recherches anatomico-pathologiques sur la cirrhose du foie*, *Arch. gén. de med.* 53: 40-79 (May) 1840.

2 Rokitsky, C. *A Manual of Pathological Anatomy*, London, C. & J. Adlard, 1849, vol. 2.

(1849) and Henle³ (1844) Budd⁴ (1857) observed that the size of the liver in certain cases of chronic valvular disease was decreased, but he was unwilling to accept this as the result of heart failure alone. He stated the belief that these changes in the liver occur only in cases in which spirits have been used excessively and that these indiscretions increase the vulnerability of the organ to the influences of chronic stasis. Budd's views were championed by Monneret⁵ (1852) and by Bamberger⁶ (1855). The literature of the ensuing years contained many conflicting opinions.⁷

In 1883 Sabourin⁸ published his classic work on chronic passive congestion of the liver. He clearly implied that he favored the concept that hepatic cirrhosis results from cardiac failure. He found that the degenerative processes as they occur in cases of chronic congestive heart failure result in capillary dilatation and trabecular atrophy. It was in these zones of atrophy about the central vein that he found the new connective tissue to be formed first. He said he believed that the sequence of events leading to sclerosis depends on a thickening and contraction of the strands of connective tissue which line the spaces about the central veins, this thickening and condensation eventually leading to the stage of central cirrhosis. He stated that this type of cirrhosis is easily recognizable, because it connects central vein to central vein or sublobular vein and thus encircles the hepatic tissue of the peripheral portion of adjacent lobules. Such an arrangement produces an apparent reversal of the usual order, the portal system at times being in the center of the lobule. Sabourin's views on the pathogenesis of these changes are well exemplified in the following quotation:

3 Henle, cited by Rolleston, H., and McNee, J. W. *Diseases of the Liver, Gall-Bladder and Bile-Ducts*, New York, The Macmillan Company, 1929.

4 Budd, G. *On Diseases of the Liver*, ed. 3, Philadelphia, Blanchard & Lea, 1857.

5 Monneret, cited by Piéry^{10b}.

6 Bamberger, cited by Piéry^{10b}.

7 (a) Cornil, V., and Ranvier, L. *A Manual of Pathological Histology*, translated by E. O. Shakespeare and J. H. C. Simes, Philadelphia, Henry C. Lea, 1880. (b) Ferricks, cited by Piéry^{10b}. (c) Forster, cited by Piéry^{10b}. (d) Ferricks, F. T. *A Clinical Treatise on Diseases of the Liver*, London, The New Sydenham Society, 1861, vol. 2. (e) Green, T. H. *An Introduction to Pathology and Morbid Anatomy*, ed. 5, Philadelphia, Henry C. Lea's Son & Co., 1884. (f) Jones, H., cited by Talamon^{7m}. (g) Klebs, cited by Talamon^{7m}. (h) Legg, W., cited by Talamon^{7m}. (i) Liebermeister, cited by Piéry^{10b}. (j) Murchison, C. *Clinical Lectures on Diseases of the Liver, Jaundice and Abdominal Dropsy*, ed. 3, London, Longmans, Green & Co., 1885. (k) Rendu, cited by Piéry^{10b}. (l) Rindfleisch, cited by Talamon^{7m}. (m) Talamon, C. *Contribution à l'étude de la sclérose hépatique d'origine cardiaque*, *Rev. de med.*, Paris **1**: 273-296, 1881.

8 Sabourin, C. *La cirrhose du système sus-hépatique d'origine cardiaque*, *Rev. de med.*, Paris **3**: 521-535, 1883.

It is sufficient for us to know that there is blood stagnation produced by cardiac affliction and that this stagnation produces capillary trabecular atrophy and finally sclerosis, and all in a very systematic manner prevailing over the hepatic venous territory, such as we understand it

Parmentier,⁹ in 1889, reported the first experimental work on chronic passive congestion of the liver. He produced chronic engorgement of the liver in animals by bringing about tricuspid regurgitation. He was not, however, able to produce hepatic cirrhosis in his experimental animals by this method. The contemporary literature contains other references antagonistic to the tenets of the existence of cardiac cirrhosis.¹⁰

Lambert and Allison,¹¹ in 1916, reviewed 112 cases of chronic passive congestion of the liver. They divided their cases according to five types as follows. In the first type there was principally capillary dilatation with atrophy of the central cells, in the second type, central degeneration with or without congestion, in the third type, a central accumulation of fat with midzone hyperemia or necrosis, in the fourth type what was described as central necrosis, usually associated with hemorrhages, and in the fifth type, "collapse fibrosis," a condition which they concluded was identical with cardiac cirrhosis. Of the last type of case they found reports of only 16 instances (14.2 per cent), the condition occurring only in the presence of chronic heart failure.

Ophuls,¹² in 1926, found in 166 cases of cirrhosis of the liver occurring in 3 000 necropsies only 22 in which the condition was typical of cardiac cirrhosis, this represents an incidence of about 0.7 per cent.

9 Parmentier, cited by Rolleston, H., and McNee, J. W. *Diseases of the Liver, Gall-Bladder and Bile-Ducts*, New York, The Macmillan Company, 1929.

10 (a) Bolton, C. The Pathological Changes in the Liver Resulting from Passive Venous Congestion Experimentally Produced, *J. Path. & Bact.* **19** 258-264, 1914-1915. (b) de Sevedavy, J., cited by Piery.^{10h} (c) Frothingham, C., Jr. Chronic Passive Congestion of the Liver, *Arch. Int. Med.* **5** 1-5 (Jan.) 1910. (d) Hanot, V. La cirrhose hypertrophique avec ictère chronique, Paris, Rueff & Cie, 1892. (e) La cirrhose de Budd, *Arch. de med.* **1** 3-20, 1899. (f) Hutchison, R., and Levy Simpson, S. Occlusion of the Hepatic Veins with Cirrhosis of the Liver, *Arch. Dis. Childhood* **5** 167-186 (June) 1930. (g) Oertel, H. Multiple Non-Inflammatory Necrosis of the Liver with Jaundice in Chronic Cyanosis, *Arch. Int. Med.* **6** 293-300 (Sept.) 1910. (h) Piéry, M. Pathogénie de la cirrhose cardiaque. Stase sanguine et sclérose du foie, *Arch. gén. de méd.* **2** 582-613 and 714-744, 1900. (i) Rossle, R., cited by Albot, G. Hepatites et cirrhoses. Classification, pathogénèse et morphogénèse des hépatites diffuses aiguës, subaiguës et chroniques d'après les notions récentes sur la physio-pathologie hépatobiliaire, Paris, Masson & Cie, 1931. (j) Salaman, R. N. The Pathology of the Liver in Cardiac Disease and Its Clinical Lessons, *Lancet* **1** 4-7 (Jan. 5) 1907.

11 Lambert, R. A., and Allison, B. R. Types of Lesion in Chronic Passive Congestion of the Liver, *Bull. Johns Hopkins Hosp.* **27** 350-356 (Dec.) 1916.

12 Ophuls, W. A Statistical Survey of Three Thousand Autopsies, Stanford University, Calif., Stanford University Press, 1926.

He defined cardiac cirrhosis as "advanced cyanotic atrophy of the liver with development of considerable new fibrous tissue"

Moschcowitz,¹³ in 1937, advanced the idea that cirrhosis of the liver occurring with chronic heart failure is the result of increased venous pressure within the hepatic area

In 1930 Zimmerman and Hillsman¹⁴ published convincing experimental data indicating that hepatic cirrhosis may result from severe chronic passive congestion. They produced partial obstruction of the thoracic portion of the inferior vena cava in dogs by means of an aluminum band

Boles and Clark,¹⁵ in 1936, found hepatic cirrhosis of all types in 6 per cent of 4,000 necropsies and stated that cardiac cirrhosis was the third most common type

The present day French view of *cirrhose cardiaque* was expressed as follows by Roussy, Leroux and Oberling¹⁶ in 1933

If the process of chronic passive congestion is prolonged, the picture becomes complicated by a process of regeneration of hepatic tissue which progresses to the production of exuberant nodules, and an adenomatous appearance is produced. By proliferation of connective tissue about the central lobular vein and around the hypertrophic islands of tissues, the surface becomes irregularly granular and hardened. The liver shrinks. On macroscopic section the area is separated cleanly into pale yellow regions on a background of liver, which is hardened and congested. That lesion corresponds to the *cirrhose cardiaque*

Roussy and his associates emphasized the fact that there are two primary views regarding the pathogenesis. One considers venous stagnation as the etiologic agent, and the other considers additional influences, such as infection and toxemia, as the etiologic agent

MATERIAL

The basis of this study was 75 cases of cardiac disease in which prolonged single or multiple episodes of congestive heart failure had occurred. Cases of congestive failure of short duration were excluded, as cardiac cirrhosis is not encountered in such instances. This fact was determined in a review of 500

13 Moschcowitz, E. Hypertension of the Pulmonary Circulation. Its Causes, Dynamics and Relation to Other Circulatory States, *Am J M Sc* **174** 388-406 (Sept.) 1927, Phleboscclerosis of the Hepatic Veins as Associated with Chronic Passive Congestion of the Liver and Cardiac Cirrhosis (Preliminary Report), in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman*, New York, International Press, 1932, vol. 2, pp. 857-875

14 Zimmerman, H. M., and Hillsman, J. A. Chronic Passive Congestion of the Liver. An Experimental Study, *Arch Path* **9** 1154-1163 (June) 1930

15 Boles, R. S., and Clark, J. H. The Role of Alcohol in Cirrhosis of the Liver. A Clinical and Pathological Study Based on Four Thousand Autopsies, *J A M A* **107** 1200-1203 (Oct. 10) 1936

16 Roussy, G., Leroux, R., and Oberling, C. *Preces d'anatomie pathologique*, Paris, Masson & Cie, 1933, vol. 1

unselected cases (Dr Boland¹⁷) of chronic passive congestion of the liver. Microscopic studies of the liver were made in each case by one of us (Dr Boland), sections being stained with hematoxylin and eosin and by the Van Gieson method. Many sections were also stained by the Mallory-Heidenhain and Perdrau technics.

Edema of the dependent portions of the body was necessary before the patient was considered as having congestive heart failure. The onset of failure was determined as accurately as possible from the first appearance of the edema (table 1).

Most of the principal forms of heart disease were represented in the etiologic array responsible for the congestive heart failure (table 2).

TABLE 1—*Single and Multiple Episodes of Congestive Heart Failure*

Single Episode, Duration of Failure, Months	No. of Cases
4-5	13
6-7	13
8-9	8
10-11	2
12+	11
Total	47
Multiple Episodes, Number of Episodes	
2-4	17
5+	11
Total	28

TABLE 2—*Causes of Congestive Failure*

	No. of Cases
Hypertensive heart disease	33
Coronary and hypertensive heart disease	1
Hypertensive heart disease and coronary thrombosis	5
Hypertensive heart disease and exophthalmic goiter	1
Severe coronary sclerosis with extensive myofibrosis	3
Coronary thrombosis	2
Rheumatic mitral stenosis (with or without mitral insufficiency)	10
Rheumatic mitral stenosis with defects of aortic valve	4
Rheumatic mitral stenosis with defects of aortic and tricuspid valves	1
Rheumatic mitral stenosis with adherent pericarditis	1
Rheumatic tricuspid stenosis	1
Calcareous (rheumatic) aortic stenosis	4
Adherent pericarditis	1
Syphilitic aortitis and aortic insufficiency, aneurysm	3
Pulmonary emphysema	3
Patent foramen ovale (huge)	2
Total	75

The ages of the patients ranged from 5 to 85 years, the average age being 55.6 years. Eighty-seven per cent of the patients were between the ages of 40 and 70. There were 56 males and 19 females, a ratio of 3:1.

The clinical history, physical findings, hospital records and laboratory data were studied in each case, and an attempt was made to correlate these findings with the pathologic changes in the liver.

GROSS FINDINGS

Ascites occurred in 89.3 per cent of the cases in which there was a single episode of congestive heart failure and in 82.1 per cent of those

¹⁷ Boland, E. W. Unpublished data.

in which there were multiple episodes. The incidence of ascites in the whole group was 86.6 per cent. Icterus was present at some time during the attack of failure in 12.7 per cent of the cases in which there was a single episode and in 17.8 per cent of those in which there were repeated episodes of cardiac failure. The incidence of icterus in the entire series was 14.6 per cent.

The average weight of the liver in cases of one protracted episode of congestive heart failure was 1,799 Gm., the estimated normal weight for this group being 1,764 Gm. The average weight of the liver in cases of recurrent attacks was 1,608 Gm., the estimated normal for this group being 1,674 Gm.

HISTOPATHOLOGIC OBSERVATIONS

According to the histopathologic observations the cases may be classified in three general groups: (1) a group of cases in which there was atrophy or necrosis or both in the hepatic lobule without evidence of condensation of reticulum or cirrhosis, (2) a group of cases in which there was atrophy or necrosis together with condensation of reticulum and thickening but without cirrhosis and (3) a group of cases in which there was actual hepatic cirrhosis.

GROUP 1—Thirty-seven (49 per cent) of the 75 cases belonged in the first group (table 3). The microscopic changes in these cases were similar to those generally described as occurring in chronic passive congestion of the liver. The atrophy or necrosis was always most marked in the central third of each hepatic lobule, especially immediately adjacent to the central vein. The degeneration decreased in degree toward the periphery of the lobule. In some cases a variable degree of necrosis was apparently superimposed on the atrophic cells of the central portion of the lobule. When necrosis predominated in the central portion of the lobule, the hepatic cells surrounding the necrotic area usually showed some degree of atrophy. In many cases the degeneration extended from central vein to central vein, giving the appearance of reversed lobulation. The degree of degeneration was variable. In 6 cases there was only a minimal amount of central atrophy. In 26 cases there was a moderate to marked degree of atrophy in the central third of the lobule, with a decreasing amount of atrophy in the middle and peripheral zones. Marked necrosis of the central cells with atrophy in the peripheral cells was present in 3 cases. In 7 cases there was marked atrophy of the cells of the central portion of the lobule with superimposed necrosis (fig. 1).

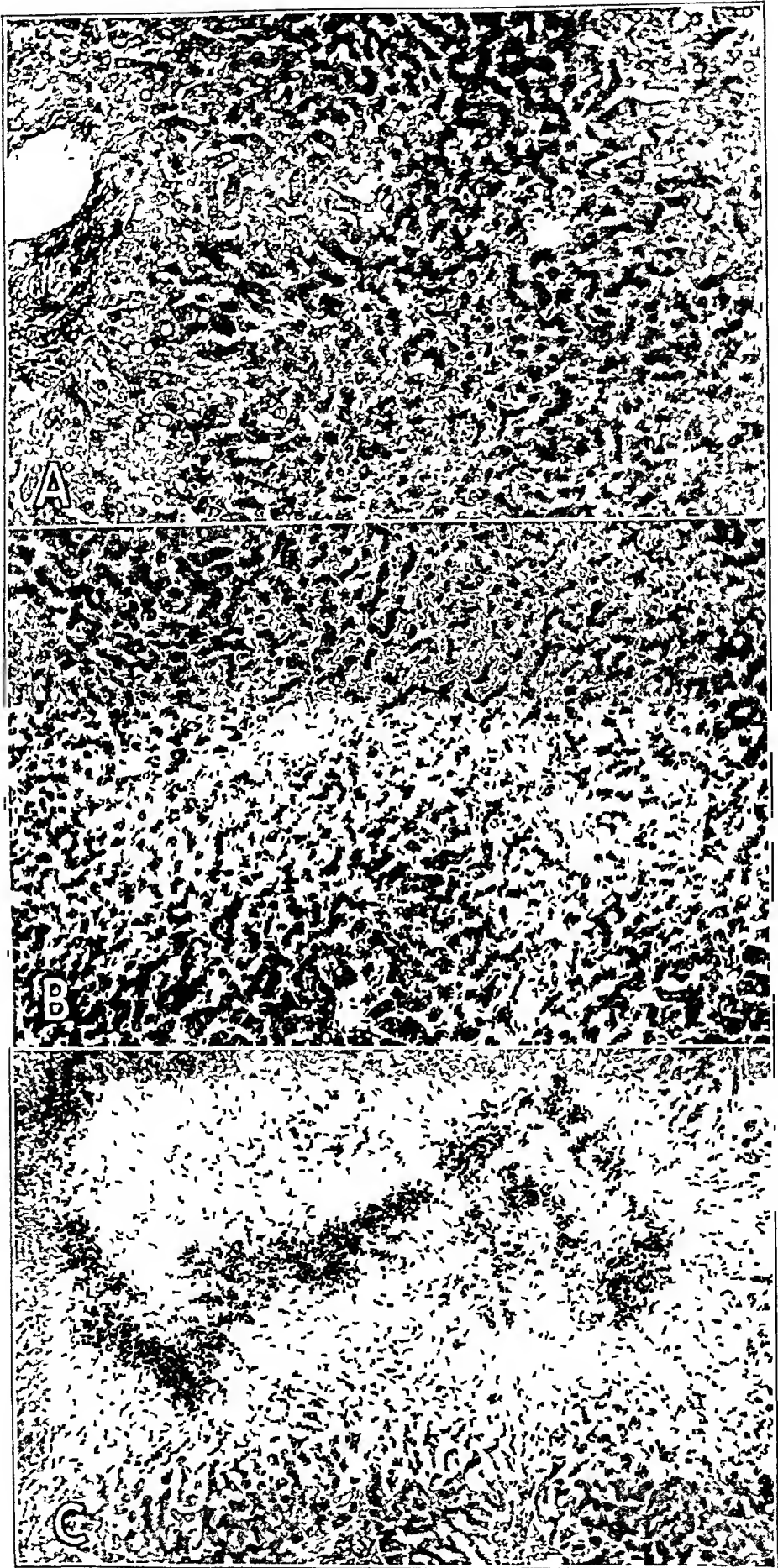


Fig 1—Atrophy or necrosis without condensation of reticulum or cirrhosis
A, a mild degree of central atrophy, *B*, a moderate degree of central atrophy,
and *C*, severe central necrosis

GROUP 2—The second group consisted of 33 cases (44 per cent) In these there was evidence of condensation of reticulum in the degenerated areas (table 4) This condensation was always most marked in the degenerated areas and seemed to vary proportionately to the degree of degeneration present However, as was observed in the preceding group, marked degeneration might occur without a condensation of reticulum The condensation appeared to result from the collapse of the central portion of the lobule as a result of the destruction of the

TABLE 3—*Group 1 Cases in Which There Was Atrophy or Necrosis or Both in the Hepatic Lobules Without Other Changes*

Single Episode, Duration of Failure, Months	No of Cases
4-5	6
6-7	9
8-9	6
10-11	2
12+	9
Multiple Episodes (Number)	
2-4	3
5+	2
Total	37 (49% of series)

TABLE 4—*Group 2 Cases in Which There Was Atrophy or Necrosis Together with Condensation and Thickening of Reticulum*

Single Episode, Duration of Failure, Months	No of Cases
4-5	6
6-7	4
8-9	1
10-11	0
12+	2
Multiple Episodes (Number)	
2-4	11
5+	9
Total	33 (44% of series)

hepatic cells in that region Close observation of the reticulum fibers revealed that they actually appeared thicker than normal This was particularly well shown when the sections were stained by the Van Gieson and Perdrau methods Reverse lobulation to some degree could be demonstrated in every case in this group The reverse arrangement was most distinct in cases of pronounced condensation of reticulum In some regions the condensed reticulum extended so distinctly from central vein to central vein that a definite band of fibers could be seen surrounding the peripheral zones of the remaining hepatic tissue, a portal radicle being located in the center of this apparently reversed lobule

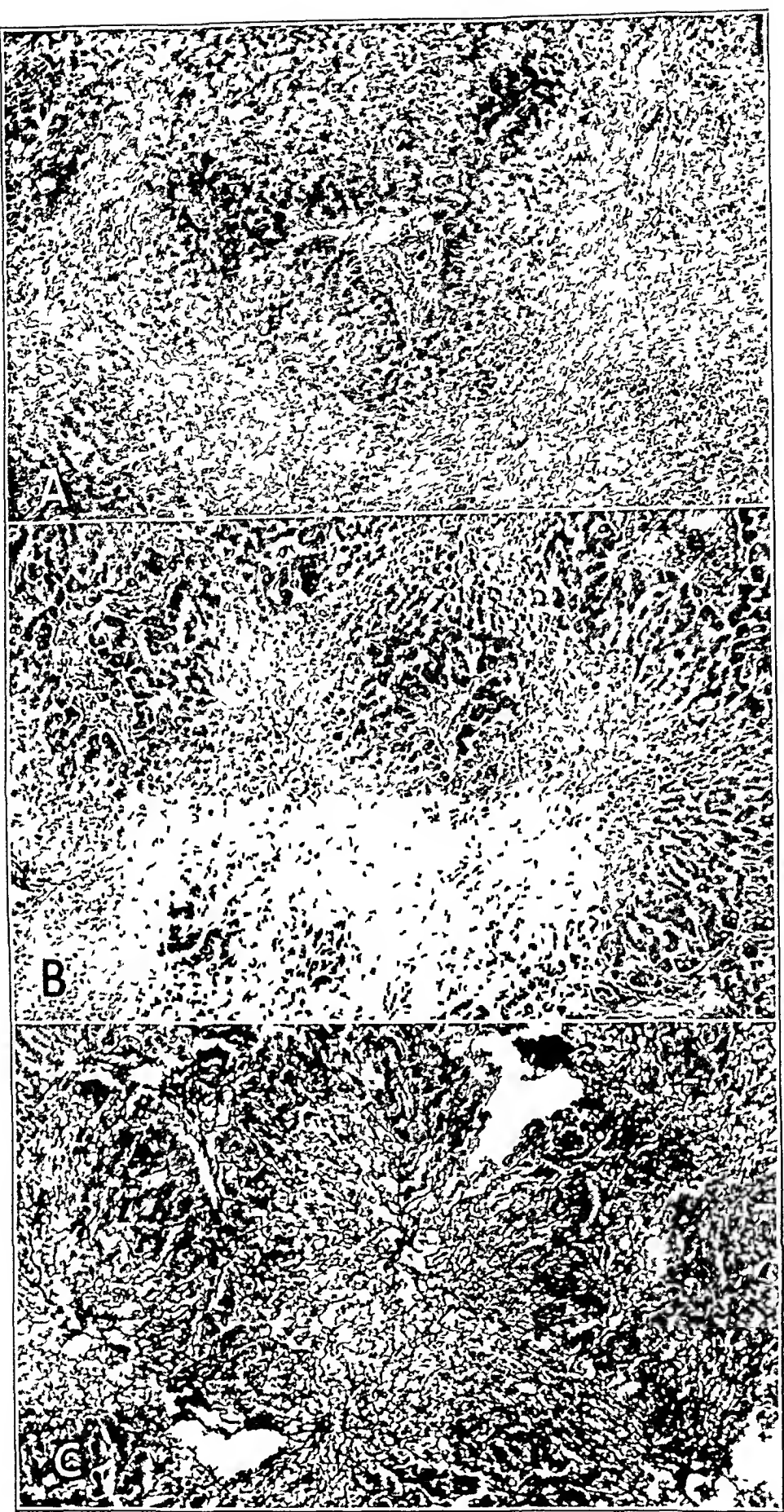


Fig 2—Condensation and thickening of reticulum but without cirrhosis *A*, a mild degree of condensation of reticulum (hematoxylin and eosin stain), *B*, a moderate degree of condensation of reticulum (note the reversed lobulation and thickening of reticulum [Van Gieson stain]), and *C*, a moderate degree of condensation and thickening of reticulum (Perdrau stain)

The degree of condensation and thickening of the reticulum varied in this group. In 21 cases the condensation was not pronounced, in 7 cases it was moderate and in 5 cases it was marked. Cases of moderate and marked degrees of condensation would probably be classified by some investigators as cases of cardiac cirrhosis. However, with careful study of the sections, no fibrous tissue proliferation was found but rather only condensation and thickening of preexisting reticulum fibers. For this reason, such cases should be designated as demonstrating condensation of reticulum resulting from chronic passive congestion rather than being classified as cases of true cirrhosis (fig. 2).

GROUP 3—In 5 cases (7 per cent) of the series there was true hepatic cirrhosis (table 5).

In these 5 cases there were marked degeneration of the central portion of the lobules and condensation of reticulum. Reversed lobulation

TABLE 5—*Group 3 Cases of True Hepatic Cirrhosis as a Result of Cardiac Decompensation*

Single Episode, Duration of Failure Months	No. of Cases
4-5	1
6-7	0
8-9	1
10-11	0
12+	0
Multiple Episodes (Number)	
2-4	2
5+	1
Total	5
	(7% of series)

was prominent. There appeared to have been almost complete destruction of entire lobules in certain scattered areas. Extensive collapse of the necrotic regions evidently occurred, and portal radicles appeared to have been caught in the massive coalescence. In these regions fibrous tissue proliferation had occurred and fibroblasts could be identified by the oil immersion method. In addition, the normal architectural arrangement of the liver was disrupted, and an increase in the number of lymphocytes was seen in some of the fibrotic areas. An apparent increase in the number of bile ducts was frequently observed. In 3 of the 5 cases there appeared to be adenomatous regeneration of hepatic tissue. The cirrhosis in these cases was not uniform throughout the sections but was scattered in an irregular manner. Between the areas of fibrosis the hepatic substance demonstrated central lobular degeneration, condensation of reticulum and reversed lobulation. At times the bands of condensed reticulum could be seen to join the areas of fibrosis. Indeed, it appeared that entire lobules had degenerated and collapsed in some regions and that these areas served as sites for the proliferation



Fig 3—True cirrhosis *A*, an area of fibrosis with an apparent increase in the number of bile ducts (note the reversed lobulation and the condensation of reticulum in the adjacent tissue [hematoxylin and eosin stain]), *B*, lower magnification, showing marked condensation of reticulum, reversed lobulation and fibrosis of the areas of massive destruction (hematoxylin and eosin stain), and, *C*, a higher magnification of the preceding section, showing fibrosis and an increase in the number of bile ducts (Van Gieson stain)

of fibrous tissue. The patchy nature of the fibrosis and the intervening regions of central degeneration and condensation of reticulum made the picture differ considerably from that usually seen in advanced portal cirrhosis.

In 1 additional case there was failure to show marked central destruction of the lobules, with reticular condensation and reversed lobulation. There was, rather, only a mild degree of central atrophy in lobules which persisted between the scattered areas of fibrosis. As will be pointed out later, in this case there were certain clinical features which indicated that the hepatic cirrhosis probably preceded the onset of congestive heart failure (fig. 3).

COMMENT

The most frequent pathologic picture seen in the liver as a result of prolonged or repeated episodes of congestive heart failure is degeneration of the central portion of the lobules, with or without condensation of reticulum. True hepatic cirrhosis is an uncommon finding.

It is generally assumed that central lobular atrophy results from chronic passive congestion of gradual onset and that necrosis develops when cardiac failure occurs more abruptly or is of greater severity. It was difficult to establish this fact from this material, it may be suggested, however, that when necrosis was apparently superimposed on preexisting central atrophy, the patient may have suffered severe terminal passive congestion. The toxic factor of Mallory¹⁸ cannot be disregarded in these cases as the cause of the severe central necrosis. It must be pointed out, however, that the clinical record and associated postmortem observations do not correspond with sufficient regularity for the definite establishment of an infectious or toxic origin for the necrosis. It is a well known fact that many toxins exert their first visible effects on the central cells of the hepatic lobule. Bollman and Mann,¹⁹ moreover,

18 Mallory, F. B. Necrosis of the Liver, *J. M. Research* **6** 264-280 (July) 1901, Chronic Passive Congestion of the Liver, *ibid* **24** 455-462 (April) 1911, cited by Boles and Clark¹⁵

19 Bollman, J. L. Experimental Cirrhosis of the Liver, *Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America*, 1929, pp. 387-390. Bollman, J. L., and Mann, F. C. Alterations in Hepatic Function Produced by Experimental Hepatic Lesions, *Ann. Int. Med.* **9** 617-624 (Nov.) 1935. Bollman, J. L., Mann, F. C., and Magath, T. B. Studies on the Physiology of the Liver. XV. Effect of Total Removal of the Liver on Deamination, *Am. J. Physiol.* **78** 258-269 (Oct.) 1926. Mann, F. C., and Bollman, J. L. Jaundice. A Review of Some Experimental Investigations, *J. A. M. A.* **104** 371-374 (Feb. 2) 1935. Bollman, J. L., and Mann, F. C. Experimentally Produced Lesions of the Liver, *Ann. Int. Med.* **5** 699-712 (Dec.) 1931.

have clearly shown that impairment of the circulation of the liver increases the effectiveness of many hepatic toxins. One cannot, therefore, deny the possibility of a coexisting toxic factor in these cases. That some factor besides passive congestion may be involved is suggested by the fact that one cannot predict from the clinical history and physical findings whether the liver will show atrophy or necrosis. The claim for the toxic factor becomes strengthened in some cases by the presence of many polymorphonuclear leukocytes in the necrotic areas. It must be remembered, however, that polymorphonuclear leukocytes may migrate to sites of necrosis regardless of its cause.

In 33 cases there was some degree of condensation of reticulum, it was minimal in 24 cases. In the remaining 9 cases the condensation was prominent, and several authors probably would have classified the cases as representing cirrhosis. These 9 cases corresponded well with the descriptions of cases of cardiac cirrhosis given by Sabourin, Salaman, Lambert and Allison, and Boles and Clark. They undoubtedly fit the descriptions of "red atrophy," "collapse fibrosis" and other terms used by some investigators as synonyms for cardiac cirrhosis. There was not, however, true cirrhosis as the term is generally understood. There were demonstrated only condensation and thickening of preexisting reticulum. In no case of this particular group was there evidence of new connective tissue proliferation, lymphocytic infiltration, adenomatous regeneration or an apparent increase in the number of bile ducts. In these cases the condition should therefore be designated as marked by condensation of reticulum and should not be included under the term cirrhosis.

It is interesting that some degree of condensation of reticulum and thickening was seen in 86 per cent of the cases of multiple episodes of congestive heart failure, whereas it occurred in only 30 per cent of the cases of protracted single episodes. The possibility that thickening of reticulum and perhaps some degree of condensation were residua of previous central degeneration becomes apparent. The thickening of reticulum may constitute the only irreversible change in the liver as a result of partial lobular degeneration resulting from chronic passive congestion. It is probable that during periods of congestive heart failure in cases in which there were repeated episodes of such failure the partially destroyed lobules regenerated almost to their normal state. Bollman and Mann have shown that if the necrosis of the lobule is not too extensive, reparative processes begin soon after removal of the toxin and that the restoration of the hepatic cells is so complete that the lobule again appears fairly normal. They said they believed that the disintegrated central hepatic cells are removed by phagocytosis, their place being taken by new hepatic cells. New cells appear to arise by division of adjacent uninjured hepatic cells. It may be emphasized

here that restoration to normal apparently does not occur when the necrosis involves an entire lobule

In 6 of the 75 cases there was true cirrhosis. In 5 the changes differed from those of the advanced portal type as a result of their patchy nature and the central degeneration, condensation of reticulum and inverse lobulation in the hepatic parenchyma between the areas of fibrosis. In 5 of these 6 cases the cirrhosis evidently developed after the onset of congestive heart failure. In the sixth case the ascites appeared to follow a severe respiratory infection and began six months prior to the onset of dependent edema. It is assumed that in this case the cirrhosis preceded the onset of congestive heart failure. This supposition, as has already been shown, is strengthened by the microscopic observations.

It is reasonable to expect that cirrhosis which develops as a result of chronic passive congestion will be seen in those cases in which there have been repeated episodes of congestive heart failure. If the passive congestion is severe enough to produce necrosis of the hepatic cells it is severe enough to prevent proliferation of fibrous tissue and adenomatous regeneration. Certainly, then, the cirrhosis must develop during periods of partial or complete restoration of cardiac function. In the 5 cases in this group, evidence seemed to be presented in support of this hypothesis. In 3 cases there was a history of repeated bouts of congestive heart failure, with intervening periods of partial recovery, in the 2 remaining cases there was a single continuous episode of failure. In each instance, however, there was a history of intervals of rest in bed, with considerable improvement in the degree of cardiac decompensation.

On the basis of the experimental work of Bollman and Mann together with the microscopic observations in these cases, it seems justifiable to postulate the mechanism involved in the production of cirrhosis. The degeneration resulting from chronic passive congestion of the liver appears to vary in its extent and severity in different lobules. Some lobules may be completely destroyed, whereas others show degeneration in only the central portion. As has already been emphasized the partially destroyed lobules probably are repaired during intervals of improvement in cardiac function to a state closely approximating the normal, a thickened reticulum remaining as the only relic. When entire lobules are destroyed the change appears to be irreversible, and the microscopic observations certainly suggest that in some areas whole lobules have been completely destroyed. In these extensively degenerated regions a collapse of the reticulum apparently has occurred. One or more portal spaces are frequently seen in the coalesced masses of reticulum. It is in these patchy areas that fibrous tissue proliferation and, at times, adenomatous regeneration of hepatic cells are observed. Bollman and Mann, in their report of cases of experimental cirrhosis,

suggested that the fibrous tissue develops from that already present about the portal spaces. This may likewise be the source of the fibrosis in these cases. The adenomatous regeneration probably proceeds from the few hepatic cells remaining in the collapsed lobules. It is conceivable, therefore, that during the intervals of partial cardiac recovery, fibrosis occurs in the areas of complete lobular destruction. In the partially destroyed lobules, repairation occurs which restores them to a state approaching normal.

The role played by toxins as a contributory agent in the production of cirrhosis is as obscure as in the cases of necrosis alone. In 1 of these 5 cases there was a history of acute catarrhal icterus which had occurred shortly before the appearance of dependent edema. Congestive heart failure in another case occurred in association with syphilitic aortitis and aneurysm. In this case a course of antisyphilitic treatment had been completed just prior to the first appearance of congestive heart failure. In the other 3 cases there was no evidence of a toxic or infectious factor.

Grossly, in 3 of the 5 cases in this group the cirrhotic liver was described as being nodular and firm. In the 2 remaining cases there were typical mottling of the "nutmeg" type and increased resistance to cutting.

Little correlation was found between the clinical history and the microscopic observations in this series of 75 cases. Ascites was present in each case of cirrhosis, but it was also found in 86.6 per cent of the entire series. Icterus was observed in 1 of the 5 cases of cirrhosis, although it occurred in 14.6 per cent of the entire series. When portal stasis is marked and engorgement of the liver occurs, jaundice not infrequently becomes evident in congestive heart failure and when associated with existing cyanosis results in a glaring and peculiar color of the skin and mucous membranes. Obviously neither ascites nor icterus can then serve as a diagnostic criterion of cirrhosis.

Hepatic function tests were made in only 3 of the 75 cases, a number too few to allow correlation. However, numerous tests have been carried out in other cases. In these cases either temporary recovery occurred or postmortem examination was not permitted. These observations indicate the fact that marked degrees of impairment of hepatic function, as expressed by the retention of dye introduced into the blood stream, are extremely uncommon. By denoting the grades of dye retention on a numerical basis (that is, grades 0 to 4) it is found that in the majority of cases retention is of grade 1 and in a smaller group of grade 2, with few exceptions higher grades of dye retention are not encountered. We are led to believe that functional impairment of the liver, as determined by laboratory methods, will for the most part serve as an index of the degree of necrosis or atrophy rather than as an index of the cirrhosis.

It is important to recall the fact that in some normal persons, especially those who are tall and slender, the edge of the liver may be palpated. Even though heart disease may exist in such cases, this finding may not indicate the presence of chronic passive congestion. Supplementary evidence, such as the presence of dyspnea, cyanosis, signs of pulmonary congestion and dependent edema, is usually requisite. It is also important to recognize the fact that the liver may become enlarged and varyingly engorged with blood in the absence of congestive heart failure. This is notably observed in some cases of pericardial effusion, particularly when the accumulation of fluid occurs rapidly and attains considerable proportions. This phenomenon is not the result of pressure downward from a fluid-laden pericardial sac but the result of compression of the orifices of the hepatic veins which open into the inferior vena cava. This appears to be caused by the accumulation of fluid in the pericardial sac, which rests on the diaphragm at the point where the inferior vena cava passes through.

When the liver becomes engorged rather rapidly, considerable persistent pain and local tenderness in the region of the organ are encountered. When the liver has had an opportunity to become adjusted to the circulatory stasis, as in cases of protracted congestive heart failure, these signs disappear.

Careful palpation of the liver in cases of chronic passive congestion usually gives important information, when there is massive ascites the examination obviously may reveal inconclusive findings. As a rule the enlarged liver is found to be firm, smooth and somewhat tender. When its surface is hard and irregular, it is almost certain that an additional condition exists, such as true portal cirrhosis or a metastatic malignant growth. Palpation, unfortunately, does not permit the positive identification of cardiac cirrhosis. The so-called pseudocirrhosis of Pick²⁰ will only be mentioned in passing. An enlarged, engorged liver that clearly pulsates is, with rare exceptions, evidence of organic changes involving the tricuspid valve.

Probably the most suggestive evidence available at this time in the clinical prediction that cardiac cirrhosis may be existent in a given case is through inference from the facts disclosed by this study. This evidence chiefly comprises the history of severe recurrent episodes of congestive heart failure over a relatively long time with intervals of improvement in cardiac function, when the liver receives some respite. However, in the clinical appraisal of the individual case, this evidence

²⁰ Pick, F. Cirrhose du foie d'origine pericardique, *Arch de med* **2** 105-107 (July) 1896, Ueber chronische unter dem Bilde der Lebercirrhose verlaufende Pericarditis (pericarditische Pseudolebercirrhose) nebst Bemerkungen über die Zuckergussleber (Curschmann), *Ztschr f klin Med* **29** 385-410, 1896.

appears to be of limited value, owing to the fact that even under these circumstances the development of true cardiac cirrhosis is uncommon

SUMMARY AND CONCLUSIONS

The usual histopathologic picture of the liver in cases of prolonged or recurrent episodes of congestive heart failure is that of central lobular atrophy or necrosis or both. Condensation of reticulum and thickening may or may not be present.

The presence of condensation of reticulum alone does not warrant the use of the term cardiac cirrhosis.

True cirrhosis, developing in the course of congestive heart failure, does occur but is rare. No definite criteria were elicited from this study whereby the development or presence of cardiac cirrhosis can be recognized clinically.

ENLARGEMENT OF THE LIVER IN DIABETIC CHILDREN

1 HIS INCIDENCE, ETIOLOGY AND NATURE

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During the past few years we have been impressed with the fact that in children with severe diabetes mellitus which has not been brought under satisfactory control, well marked enlargement of the liver may occur. In this paper we are reporting studies of 60 children (54 living and 6 dead) with pronounced hepatomegaly from among 1,077 patients (815 living and 262 dead) in whom the onset of diabetes occurred at the age of 15 years or under, the list as here presented is not complete. In view of the large number of cases we regard enlargement of the liver as one of the outstanding complications of uncontrolled severe juvenile diabetes. The cause of the increase in size, the nature of the enlargement—whether fatty, glycogenous or otherwise—and the specific treatment present difficult and interesting problems.

As Hanssen¹ has pointed out, little mention of gross hepatomegaly in human diabetes is to be found in the literature. He cited Umber² and von Noorden and Isaac³ as referring to this complication. It is true that as early as 1748 Mead⁴ called attention to fatty infiltration of the liver in diabetes. Adlersberg and Porges⁵ said they considered an enlarged and fatty liver a regular finding. In his text on diabetes

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1 Hanssen, P. Enlargement of the Liver in Diabetes Mellitus, J A M A **106** 914 (March 14) 1936

2 Umber, F. Ernährung und Stoffwechselkrankheiten, ed 3, Berlin, Urban & Schwarzenberg, 1925

3 von Noorden, C, and Isaac, S. Die Zuckerkrankheit und ihre Behandlung, ed 8, Berlin, Julius Springer, 1927

4 Mead, R, cited by Widnas, K. Etudes sur le diabete sucre chez l'enfant, Uppsala, Almqvist & Wiksells, 1928

5 Adlersberg, D, and Porges, O. Zur Theorie und Praxis der kurativen Diabetesbehandlung, Klin Wchnschr **5** 1451 (Aug 6) 1926

Naunyn⁶ stated that "in man one finds, as already described by Klebs marked fatty infiltration of the liver."

In a monograph published in 1926 Priesel and Wagner⁷ stated that they had repeatedly observed enlargement of the liver in children with uncontrolled diabetes. They said they regarded the increase in size as due to fat and found that there was a tendency for the organ to return to normal with improvement in the diabetic condition. In 1932 one of us (P. W.)⁸ recorded the fact that at autopsy, fatty infiltration of the liver was present in 7 diabetic children. Furthermore, mention was made of roentgenologic evidence in a living patient (case 14) of a decrease in size of an enlarged (and presumably fatty) liver with institution of careful treatment of the diabetes. The complication has probably escaped general notice in the past because it is encountered chiefly in cases of severe, poorly controlled diabetes. These occur particularly in children, and in the pre-insulin days such patients usually lived for only a few weeks or months and so escaped prolonged observation and study.

A case of the type described in this paper was reported by Mauriac⁹ in 1934. His patient was a dwarf with a large abdomen, and in this case a collateral circulation developed in the abdominal wall.

PRESENTATION OF DATA

We have made special studies of 60 patients with well marked enlargement of the liver.¹⁰

Sex—Although the patients were not selected with this point in mind, there was an equal number of boys and of girls, 30 each.

Age—The average age of the 54 living patients was 14.9 years in January 1937. The average age in the 6 fatal cases at death was 18.7 years.

Duration of Diabetes—The age at which the enlargement of the liver was first noted varied from 4 to 21.1 years, with an average of 11.9 years. On the average, five and seven-tenths years elapsed from the time of the onset of diabetes until the enlargement of the liver was

6 Naunyn, B. *Der Diabetes melitus*, ed. 2, Vienna, A. Holder, 1906, p. 284.

7 Priesel, R., and Wagner, R. *Die Pathologie und Therapie der kindlichen Zuckerkrankheit*, *Ergebn. d. inn. Med. u. Kinderh.* **30**: 536, 1926.

8 White, P. *Diabetes in Childhood and Adolescence*, Philadelphia, Lea & Febiger, 1932, p. 169.

9 Mauriac, P. *Hépatomegalies de l'enfance avec troubles de la croissance et du métabolisme des glucides*, *Paris méd.* **2**: 525 (Dec. 29) 1934.

10 To save space a table (table 1) which presents the data concerning these patients in detail appears only in the reprints.

noted The average period of observation of the living patients after the discovery of hepatomegaly was three and six-tenths years

Type of Dietary Treatment—The great majority of these patients had been supposedly receiving diets with a carbohydrate-fat ratio of 2 : 1 As a matter of fact, many of them had paid scant attention to dietary restrictions, eating irregularly and freely The cases are therefore, by and large, ones of uncontrolled diabetes

As an indication of the type of diet now prescribed in such cases, actual average figures for the diets of the boys and girls at a camp during the summer of 1936 (approximately 200 children) are given in the following tabulation

Age, Yr	Carbohydrate, Gm	Protein, Gm	Fat, Gm	Calories	Calories per Kg. of Body Weight
0-5	163	64	72	1,556	82
6-10	196	84	87	1,885	67
11-15	215	98	95	2,107	51
16-20	221	99	88	2,072	38

Severity of Diabetes—As an index of the severity of the diabetes one may point to the average (highest) blood sugar value during fasting for the group (living patients), 0.38 per cent and average dosage of insulin, 48 units a day

Complications—Nothing attests so convincingly to the severity and the lack of control of the diabetes of these young patients as an enumeration of the diabetic complications found in the group Of the 54 living patients, 38 had had one or more attacks of severe acidosis or coma, 42 had had frequent attacks of severe hypoglycemia, 26 were true dwarfs, being 4 inches (10 cm) or more below the standard height for their age, 14 others had infantilism without dwarfism, 9 had arteriosclerosis, as evidenced by sclerosis of the retinal vessels or roentgenologically visible calcification of the arteries of the legs, 1 had cataracts, 7 had had peripheral neuritis, 3 had or had had active tuberculosis, and 15 had had persistent or recurring infections particularly of the skin or urinary tract All the 6 children who died had had severe acidosis or coma at some time during their diabetic life, and in 3 instances coma was the primary cause of death Four of the 6 were true dwarfs, 4 had arteriosclerosis, 1 cataracts, 1 tuberculosis and 2 severe infections other than tuberculosis One patient died of pulmonary tuberculosis and another of pneumococcic meningitis

When the statistics were analyzed as to sex, it was apparent that this was not an important factor and that except for abdominal pain and splenomegaly, which occurred almost twice as commonly in the girls as in the boys, the incidence of complications was strikingly similar for the two sexes

Size of the Liver—The enlargement of the liver in the cases under discussion was a real factor, not a questionable or transient increase in

size In most instances the edge of the liver could be felt to descend on inspiration to well below the level of the umbilicus in the mamillary line By roentgenogram the tip of the liver could be seen to lie in 18 of the 60 cases, at one time or another, in the pelvis and in 3 other cases just at the level of the iliac crest In many cases the edge of the liver felt firm and hard and it was often tender The first change noted in the cases in which a decrease in size took place was a softening in consistency, as judged by abdominal palpation With 1 possible exception no cases of ascites were encountered

In 31 instances enlargement of the spleen was noted either by palpation or roentgenographically The roentgenograms showed no enlargement of the kidneys except in 5 cases (cases 12, 14, 56, 57 and 60), but even in those cases the increased size of the shadow was questionable (as in case 57) or slight In 2 of the 5 cases in which the kidneys were seen post mortem (cases 56 and 60) the size was found to be well within normal limits In none of the 60 cases was enlargement of the heart demonstrated Hence one can state that in these children with hepatomegaly, although some enlargement of the spleen took place in about half of them, enlargement of the kidneys or of the heart was not characteristic

Hepatic Function—As judged by the usual tests, there was no impairment of hepatic function except in 2 cases In 1 case (case 10) there was acute catarrhal jaundice, with a plasma bilirubin value as high as 5.6 mg per hundred cubic centimeters in January 1937, in the other case (case 21) the patient was acutely ill with diabetic coma and hepatitis with jaundice in May 1936 Aside from these 2 cases, determinations of the plasma bilirubin content in 8 other cases yielded values uniformly within a normal range, with figures varying from a trace to 0.3 mg per hundred cubic centimeters (In case 25 a value of 0.8 mg was obtained on one occasion) Our data in this respect are inadequate and in view of the experience of Rabinowitch¹¹ should be amplified He reported an average value of 0.86 units for one hundred and thirteen tests carried out on 10 patients In 6 of our patients on whom the bromsulphalein test was carried out, no delay in the removal of the dye from the blood stream was noted Furthermore, in only 1 of 30 cases in which complete determinations of free, combined and total cholesterol were made did a significant lowering of the ratio of cholesterol ester to total cholesterol occur (table 1) Accordingly, although in this condition there is undoubtedly some impairment of hepatic function as regards carbohydrate and fat metabolism, the tests available were

11 Rabinowitch, I. M. Effects of Betaine upon the Cholesterol and Bilirubin Contents of Blood Plasma in Diabetes Mellitus, *Canad. M. A. J.* **34**: 637 (June) 1936

inadequate to demonstrate this probable diminution in function in the patients studied

Signs and Symptoms—Because of the huge size of the liver, in most of these children (44 of 60) the abdomen was large and protuberant. The general effect was heightened in many cases by the fact that the children were underheight, 30 of the 60 being diabetic dwarfs. Bouts of abdominal pain were of relatively frequent occurrence, having been noted in 55 per cent of the group under discussion. This was at times so severe as to lead to a surgical consultation, because of the possibility of an acute intra-abdominal surgical condition. Indeed in case 15 of the series the patient, while in a neighboring hospital, was operated on for acute disease of the gallbladder because of just such an attack of pain accompanied by mild fever and leukocytosis. At operation no abnormality of the gallbladder was made out. The enormous size of the liver was verified, but unfortunately no biopsy was made. One other patient (case 9) was operated on at the New England Deaconess Hospital because of abdominal pain, but only the enlarged liver and calcified lymph nodes were evident. Still another patient (case 21) was admitted to the hospital in diabetic coma with marked abdominal pain, fever and jaundice. He was very ill for several days, with the signs and symptoms of hepatitis, but gradually improved and is alive and reasonably well today. This case has been reported elsewhere¹²

We have attributed the abdominal pain in many of these cases to stretching of the hepatic capsule and of the accompanying visceral peritoneum.

Hematologic Findings—Enumerations of the erythrocytes and of the leukocytes, together with the determination of the hemoglobin values and (in some instances) studies of stained blood smears, were made almost as a routine. Since no significant abnormalities were evident, these data are not reported in detail.

Gastric Acidity—In 8 cases gastric analyses were carried out, an alcohol test meal (and in some instances, also histamine) being used. In 2 cases (cases 12 and 25) no free hydrochloric acid was found. Further observations need to be made to warrant conclusions.

Analyses of Duodenal Contents—Through the courtesy and cooperation of the late Dr. Lee MacPhee and of Miss Alison T. Fernald, formerly of the Evans Memorial Hospital, we were able to make analyses of the duodenal contents of 7 of the patients. The procedure used was as follows:

¹² Root, H. F. Diabetic Coma and Acute Pancreatitis with Fatty Livers [case 5], J. A. M. A. **108** 777 (March 6) 1937.

A duodenal tube was passed and its position checked roentgenographically. After the duodenal contents during fasting had been obtained, a fat meal, consisting of 5 cc of oleic acid, followed by 25 cc of warm water, was introduced through the tube. After a rest period of fifteen minutes, during which the tube was shut off, the clamp was released and the tube allowed to clean itself of oleic acid. Then, collection of B bile was begun and carried out until a definite and marked change in color occurred in the material secured. At this point the collecting flask was replaced by another and the collection continued. The latter material was designated C bile. Analyses of the enzyme content were carried out on samples of C bile as well as on those of B bile according to the methods devised by McClure¹³

The results of the analyses are given in table 2. Because of his large experience in this field, the results were shown to Dr C W McClure, who made the following statement: "The figures are suf-

TABLE 2—*Analyses of Duodenal Contents*

Characteristics	Low Normal Values	Case Numbers						
		15	37	36	33	30	28	20
B Bile								
Volume, cc		120	28	8	22	75	25	14
Time for collection, min		100	25	7	25	16	10	14
Amylolytic activity	1.0	1.8	2.2	1.1	0.5	0.6	0.6	0.7
Proteolytic activity	2.0	2.2	2.3	1.1	1.0	1.0	1.1	0.7
Lipolytic activity	1.0	1.6	0.7	0.9		1.4	2.1	1.1
C Bile								
Volume, cc			51		11	17	55	20
Time for collection, min			12		15	30	15	30
Amylolytic activity	2.0		0.0		0.3	0.5	0.0	0.0
Proteolytic activity	2.0		0.8		1.0	1.0	0.6	0.3
Lipolytic activity	1.0		0.1		1.0	1.3	0.0	0.0

ficiently abnormal to denote mild to well marked functional disturbance in the external pancreatic functions of enzyme secretion."

COMMENT

Our assumption has been that the enlargement of the liver in these cases is due primarily to extensive infiltration and deposition of fat. There are those, however, who have attributed it to marked deposition of glycogen somewhat similar to that found in von Gierke's disease. There is something to be said in favor of this view. This is outweighed in our opinion by the evidence—admittedly indirect—that the large liver is primarily filled with fat, and in the following paragraphs this evidence will be presented. We do not deny that the liver is probably also

13 McClure, C W, Wetmore, A S, and Reynolds, L. New Methods for Estimating the Enzymatic Activities of Duodenal Contents of Normal Man, *Arch Int Med* **27** 706 (June) 1921. McClure, C W, Mendenhall, W L, and Huntsinger, M E. Studies in Liver Function. IV. A Procedure for the Uniform Stimulation of the Biliary Flow, *Boston M & S J* **193**:1052 (Dec 3) 1925. McClure, C W. Functional Activities of the Pancreas and Liver, New York, Medical Authors' Publishing Company, 1937.

well filled with glycogen, indeed, our experience suggests that this is true

Postmortem Data—To find records of postmortem data for juvenile diabetic patients with marked hepatomegaly is more difficult than one would anticipate. In 4 of our 6 fatal cases an autopsy was performed. Unfortunately the interpretation of the findings was made difficult in 2 of the cases because of marked accompanying infection which in itself may cause fatty changes in the liver. The data as regards the liver in these cases are as follows

CASE 55—A boy aged 16 years, who weighed 66 pounds (30 Kg) when dressed, died in diabetic coma. Microscopic examination showed fine vacuoles of fat in the endothelium of the sinusoids. The hepatic cells were vacuolated.

CASE 56—A woman aged 23.6 years, who weighed 92 pounds (42 Kg), died of pneumococcal meningitis. The liver weighed 1,900 Gm. It was light reddish brown and mottled with yellow. The capsule was smooth. On section the liver was soft and friable, with yellowish mottling, and the cut surface was greasy. The gallbladder was normal and contained approximately 80 cc of thin, golden-brown bile. The bile ducts were patent. Microscopic study showed fine vacuolation of many of the hepatic cells. The periportal nuclei were vacuolated.

CASE 58—A boy aged 14.8 years, who weighed 40 pounds (18 Kg), died of extensive pulmonary tuberculosis. The liver weighed 1,520 Gm. The surface was brownish and mottled with reddish foci. On section the edges everted slightly. The cut surface was yellowish brown, showed slight congestion around the central vein and was markedly greasy. The gallbladder was normal, and the bile ducts were patent. There were no stones. Microscopic examination showed extensive fatty and glycogenic infiltration. There was marked congestion around the central vein. Round cell infiltration of periportal spaces was noted. There were foci of necrosis with Langhans' giant cells.

CASE 59—A girl aged 16.8 years, who weighed 106½ pounds (48 Kg), died in diabetic coma. The liver seemed rather large and weighed 1,980 Gm. It was yellowish but mottled with red spots and stripes. On section it was uniformly yellowish, with little more than a suggestion of red stripes around the lobules. A yellowish nodule was seen in the parenchyma. Microscopically the hepatic cells showed marked fatty and granular degeneration. Many of the nuclei were large and hyalinized, giving the picture usually produced by glycogenic degeneration.¹⁴

Aside from the data in these 4 cases, we have been able to collect little information regarding pathologic observations in the disorder under discussion. Until the recent publication of the paper by Brian, Schechter and Persons,¹⁵ we had found no report in the literature, and no pathologist with whom we had spoken or corresponded

14 The data were furnished by the New York Hospital. Further details of the postmortem observations are given in another report (Ralli, E. P., and Waterhouse, A. M. Diabetic Coma Occurring Nineteen Times in the Life of a Patient with Diabetes Mellitus, *J. Lab. & Clin. Med.* **18** 1119 [Aug.] 1933).

15 Brian, E. W., Schechter, A. J., and Persons, E. L. Unusual Glycogen Storage in a Case of Diabetes Mellitus, *Arch. Int. Med.* **59** 685 (April) 1937.

had had a suitable record in his files. It is generally conceded, as already mentioned, that fatty infiltration of the liver may be found in diabetic patients at autopsy, but it is difficult to find published reports of cases in which the subject was a diabetic child with hepatomegaly (without complications such as infections).

The case reported by Brian, Schechter and Persons was that of a 24 year old man with poorly controlled diabetes of over four years' duration who died in severe acidosis. At the postmortem examination the liver was large (weight, 2,700 Gm), and "the cut surface was waxy yellow and swollen". From a microscopic study of stained sections and from the fact that after eighteen months' storage in an aqueous preserving fluid (containing a dilute solution of formaldehyde U S P 1:100) the glycogen content of the liver was found to be 3.18 per cent, Brian and his associates concluded that the hepatomegaly in their patient was due chiefly to glycogen. Chemical analyses carried out recently in our own laboratory on a portion of this liver (sent to us by Dr. W. D. Forbus, of the department of pathology of Duke University) gave a value for total lipid of 8.95 Gm per hundred grams of dried hepatic substance (calculated as oleic acid). Although one may well question the validity of such a determination, made after the specimen had been in a preserving fluid for months, a figure as low as this supports the contention of Brian, Schechter and Persons that in their patient the enlargement of the liver was not due to fat. It is only fair to state, however, that review of the microscopic sections in this case by Dr. Shields Warren, of the department of pathology of the Harvard Medical School, suggested that in the enlargement hydropic degeneration may have played a large part.

Biopsies—Abdominal exploration with biopsy of the liver has not been carried out for any of our patients. No report in the literature has come to our attention except the recent one of Stetson and Ohler.¹⁶ Their patient was a 12 year old boy with diabetes, enlargement of the liver and spleen, ascites, jaundice and mild fever. There was, therefore, definite hepatitis, and the situation was not strictly comparable to that in the cases reported in this paper. It is important to note, however, the statement of Stetson and Ohler that "microscopic examination of a section of this tissue (removed at biopsy) stained with Best's carmine showed essentially normal liver structure with a tremendous amount of intracellular glycogen. The nuclei contained no glycogen, and there were but small amounts scattered about in the connective tissue." No signs of increase in fat deposits were seen. No chemical analyses for glycogen or fat were made.

¹⁶ Stetson, R. P., and Ohler, W. R. Hepatomegaly and Jaundice in a Juvenile Diabetic, *New England J. Med.* **217**: 627 (Oct. 14) 1937.

Analogy from Depancreatized Dogs—Investigators have long observed that in totally depancreatized dogs the liver is likely to become large and filled with fat. Thus Naunyn,¹⁷ in 1906, wrote as follows

In scarcely a single dog among the great number which I have seen die of severe diabetes following complete extirpation of the pancreas have I missed marked fatty infiltration of the liver, among these animals were many without infection, to which Sandmeyer said he was inclined to attribute it. Such livers can be compared macroscopically with those in the most severe cases of

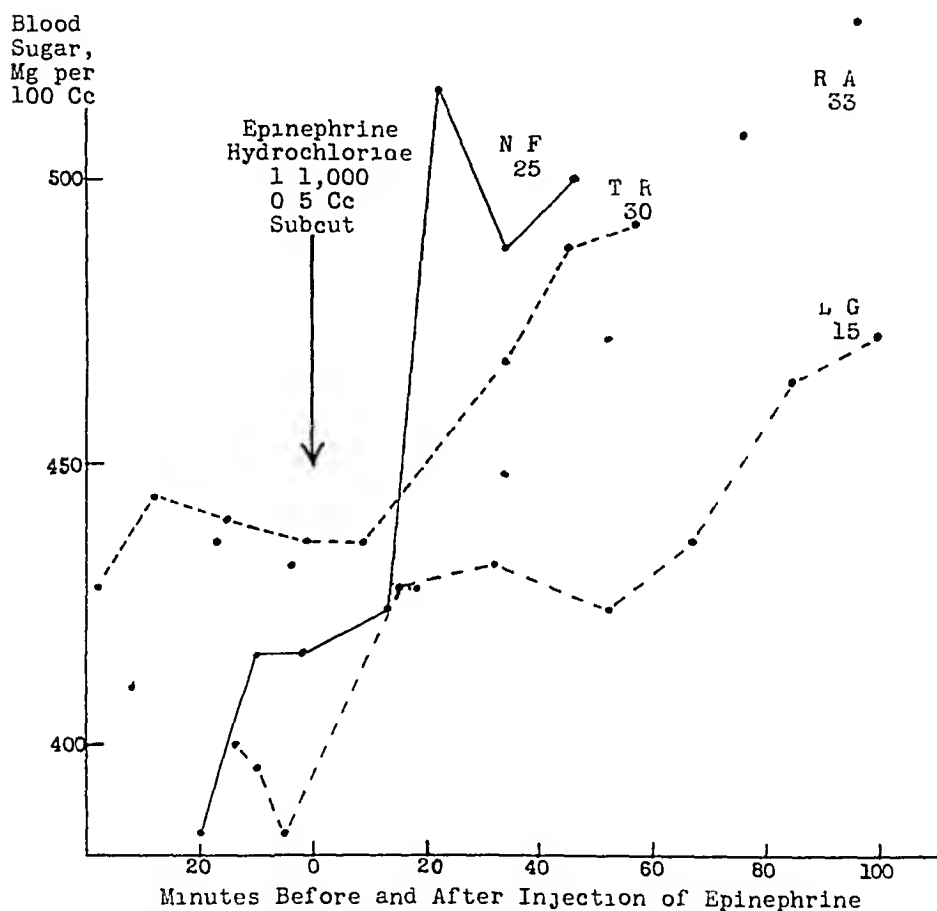


Chart showing blood sugar (capillary) curves obtained after the subcutaneous administration of 0.5 cc of epinephrine hydrochloride (1:1,000) subcutaneously. The results for 3 other patients (cases 5, 7 and 28) were essentially the same. All the patients were resting in bed throughout the making of the tests and had received no food or insulin for ten hours. In 5 of the 7 cases control tests were carried out on other days with conditions exactly the same except that no epinephrine was given. These control curves in no instance showed a rise in blood sugar content exceeding 28 mg per hundred cubic centimeters over the period covered by the experiment.

acute phosphorus poisoning in man or with the livers of fattened geese—so large, so bright yellow and so friable are they. The microscope shows the cells to be

¹⁷ Naunyn,⁶ p 118

remarkably filled with fat The weight of the liver is enormous, I found livers weighing over 1 Kg in dogs of approximately 10 Kg

The characteristic observation so vividly described by Naunyn is a strong argument in favor of the contention that the hepatomegaly in juvenile diabetes is primarily due to fat

As will be discussed in detail in our next paper, this fatty enlargement of the liver in depancreatized dogs does not occur if sufficient insulin is given to control the diabetes and if raw pancreas, lecithin or choline is added to the diet¹⁸

Differences from von Gierke's Disease—It is characteristic of glycogen storage (von Gierke's) disease that the persons affected exhibit little or no rise in blood sugar content after the injection of epinephrine and are extremely sensitive to insulin. Our patients showed normal responses to epinephrine hydrochloride (four typical curves are shown in the accompanying chart) and were no more sensitive to insulin than is the average child with severe diabetes

Furthermore, one thinks of an excess of stored glycogen as occurring with an excess of insulin in the body. In our cases of diabetes with hepatomegaly, a gross lack of insulin was characteristic

Coexistence of Glycogen and Fat in the Liver—It must be remembered that large amounts of glycogen and fat may coexist in the liver. The presence of a large amount of fat in the liver of the diabetic child does not preclude the presence of an amount of glycogen which approaches the normal. Thus in cases of glycogen storage (von Gierke's) disease, Krakower¹⁹ observed marked fatty infiltration accompanying the abnormal deposit of glycogen

CONCLUSION

Our chief purpose in this paper has been to present the clinical and laboratory findings for a sizable group of diabetic children with hepatomegaly. In the discussion we have, in general, supported the view that the primary cause of the enlargement of the liver is usually the deposition of fat rather than that of glycogen. We freely admit that the evidence is largely indirect and not supported by the observations in 2 cases reported by others, 1 at autopsy¹⁵ and 1 at biopsy,¹⁶ which most nearly resemble those presented here. We still hold to the belief, however, that fat is more reprehensible in this connection than is glycogen. We consider it possible that, in addition, a large role may be played by degenerative changes in the hepatic cells leading to imbibition of

18 Best, C. H. The Role of the Liver in the Metabolism of Carbohydrate and Fat. III. The Deposition of Liver Fat, *Lancet* **1** 1274 (June 16) 1934

19 Krakower, C. The Lipoid Factor in Glycogen Storage Disease, *J. Pediat* **9** 728 (Dec) 1936

fluid and hydropic swelling. This is supported by Warren's interpretation (referred to previously) of the tissue from the patient reported on by Brian, Schechter and Peisons¹⁵. Warren has pointed out also that the frequent occurrence of abdominal pain in these children is a point in favor of an acute swelling, which might take place more quickly from hydropic degeneration with retention of water than from deposition of fat. Kaplan and Chaikoff²⁰ have shown that a measurable amount of water does not accompany the storage of either glycogen or fat in the liver. In our own cases, possibly a primary deposition of fat was followed by hydropic degeneration with rapid retention of water, causing stretching of the hepatic capsule and acute pain.

Fortunately the problem is not insoluble. One needs only careful histologic and chemical studies of the liver in a sufficient number of suitable cases. We hope that the present report may stimulate interest in the subject so that collection of such data may be furthered. In this connection it is well to call attention to the undesirability of drawing too definite conclusions from small slices of liver obtained at biopsy, since there may be a great deal of variation between one area and another.²¹

SUMMARY

Attention is called to gross enlargement of the liver in children with severe, poorly controlled diabetes, and detailed findings in 60 cases are presented. An enlarged spleen was noted in 31 cases.

The series is noteworthy for the frequency of complications, including diabetic coma and acidosis, hypoglycemic attacks, dwarfism, arteriosclerosis, neuritis, tuberculosis and other infections, chiefly of the skin and urinary tract.

Dwarfism, a protuberant abdomen and bouts of abdominal pain were particularly striking features.

Evidence is presented to support the view that the enlargement in such cases is primarily due to gross fatty infiltration. The condition is considered as one apart from glycogen storage disease, although the presence of glycogen in amounts approaching the normal is not denied. The possible role of hydropic degeneration with retention of water is discussed.

20 Kaplan, A., and Chaikoff, I. L. The Relation of Glycogen, Fat and Protein to Water Storage in the Liver, *J. Biol. Chem.* **116** 663 (Dec.) 1936.

21 Chaikoff, I. L., and Kaplan, A. The Distribution of Fat in the Livers of Depancreatized Dogs Maintained with Insulin, *J. Biol. Chem.* **119** 423 (July) 1937.

ENLARGEMENT OF THE LIVER IN DIABETIC CHILDREN

II EFFECT OF RAW PANCREAS, BETAINÉ HYDROCHLORIDE AND PROTAMINE INSULIN

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In the preceding paper we¹ discussed the general characteristics of hepatomegaly as seen in 60 diabetic children possessing this complication. The present report is concerned with the results of treatment with three agents, raw pancreas, betaine hydrochloride and protamine insulin.

METHODS

All the children were kept under close observation, and most of them spent one or more weeks in the hospital during the period of study. For the greater part of the time, however, the patients were at home, because of the expense and undesirability of prolonged hospitalization. One must accept the fact that the care taken by the patients and their families as regards diet and insulin probably varied somewhat from time to time, so that strictly comparable conditions throughout cannot be claimed. It is most likely that during the periods of special medication, as with betaine and with protamine insulin, more care was given also to other details of treatment, thus favoring better general control of the diabetic condition.

At first roentgenographic examinations of the abdomen regarding the size of the liver were made at frequent intervals—as often as every week, but in the study of the patients taking betaine it soon became apparent that changes would take place only over longer periods. Hence, roentgenographic studies were made only at intervals of three or more months. (Later experience with protamine insulin showed, however, that changes in size might occur in a much shorter length of time.) All the roentgenograms were taken in the same laboratory.

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1 Marble, A, White, P, Bogan, I K, and Smith, R M. Enlargement of the Liver in Diabetic Children. I. Its Incidence, Etiology and Nature, Arch Int Med, this issue, p 740.

under standard conditions, and all the measurements were made by the same roentgenologist (I K B). In order to obtain values of as great accuracy as possible, the following precautions were observed: 1 The same target-film distance was used in all cases. 2 Care was taken to place the apparatus and the patient so as to allow the central ray to pass through a fixed measured point on the anterior abdominal wall. 3 The exposure was made always at the end of a full inspiration.

In establishing the size of the liver three measurements were taken: (1) the vertical diameter, (2) the long diameter, from the tip of the right lobe to the most distant point along the upper margin, and (3) the angle made by the tip of the right lobe. The liver was considered (1) unchanged in size if the variations of the vertical and long diameters were under 1 cm and if the change in the angle was less than 5 degrees, (2) slightly increased or decreased in size if the variations of the vertical and long diameters were from 1 to 1.9 cm and if the change in the angle was between 6 and 10 degrees, (3) moderately increased or decreased in size if the variations in the vertical and long diameters were from 2 to 2.9 cm and if the change in the angle was between 11 and 15 degrees, and (4) markedly increased or decreased in size if the variations in the vertical and long diameter were 3 cm or over and if the change in the angle was more than 15 degrees.

For the studies of lipids, blood was withdrawn whenever possible with the patient in the fasting state. Potassium oxalate was used as an anticoagulant. The plasma was separated and the alcohol-ether extract made as soon as possible after the withdrawal of the blood, in most cases in less than two hours. The total cholesterol value was determined by the method of Bloor,² and free and ester cholesterol values were determined by the procedure suggested by Smith and Marble.³

The betaine hydrochloride used was chemically pure and was prepared especially and furnished without cost by Merck & Co., Inc.

RESULTS

(a) *Raw Pancreas*—Two patients, a boy of 13 years (case 30) and a girl of 19 years (case 15), were noted to have enormous enlargement of the liver. The diabetes, which in the first case was of over nine years' and in the second of over six years' duration, had in each instance been continuously poorly controlled. For a period of ten to eleven weeks each patient was given 120 to 125 Gm of finely ground, fresh raw pancreas daily, usually in cold tomato juice. Frequent physical and roentgenologic examinations showed no diminution in the size of the liver. As may be seen from table 1, no significant change was produced in the level of blood cholesterol or in the percentage of the ester

² Bloor, W. R. The Determination of Small Amounts of Lipid in Blood Plasma, *J Biol Chem* **77** 53 (April) 1928.

³ Smith, R. M., and Marble, A. The Colorimetric Determination of Free and Combined Cholesterol, *J Biol Chem* **117** 673 (Feb.) 1937.

fraction Because of the essentially negative character of these results and the distastefulness of the raw pancreas, this form of experimental therapy was given up, and attention was directed to betaine

(b) *Betaine Hydrochloride*—Twelve children were given betaine hydrochloride over a period of from eight to nineteen months, usually 3 Gm daily Seven of these patients cooperated well and took the betaine as prescribed, the other 5 took it irregularly For part of the period the betaine was mixed with the food, and for part it was administered in capsules No difference was noted in the results secured To a control group of 6 children with similar enlargement of the liver no betaine was given In tables 2 and 3 the results obtained are summarized (see also the general summary given in table 5)

TABLE 1—*Effect of Raw Pancreas on the Cholesterol Content of the Blood in Two Cases*

Date, 1935	Cholesterol				Comment
	Free, Mg per 100 Cc	Ester, Mg per 100 Cc	Total, Mg per 100 Cc	Ester in Total, Percentage	
Master T R (case 30)					
March 17	68	170	238	71	125 Gm of raw pancreas daily from Feb 23, to May 10, 1935
April 11	64	135	202	69	
May 14	83	164	246	66	
July 15	85	143	228	63	
Miss L G (case 15)					
March 6			225		120 Gm of raw pancreas daily from March 12, to at least June 7, 1935
April 9	65	156	211	69	
August 5	67	156	219	71	

It will be noted that whereas only 1 of the 6 patients in the control group showed a diminution in the size of the liver during the period of special study, 6, or 50 per cent, of those receiving betaine showed such a decrease Thus there seems to have been some effect attributable to the betaine As we followed the studies closely, however, we were not impressed by any sudden or dramatic decrease in the size of the liver Such effect as was secured did not impress us as a definite response to a specific remedial agent Moreover, it is entirely possible that some of the beneficial results seen in the patients taking betaine was due to the fact that greater care was taken by them as regards diet and insulin, because of the common experience that whenever a special type of treatment is introduced there is often greater attention to other details

There was little or no effect on the plasma cholesterol free, ester or total, as may be seen in table 2

TABLE 2—Effect of the Oral Administration of Betame Hydrochloride on the Size of the Liver and the Plasma Cholesterol Content

Case No., Jan 1, 1937	Sex	Age on Jan 1, 1937	Severity of Diabetes		Usual Daily Dose of Insulin Units	Administration of Betaine		Size of Liver†							Summary of Results	Plasma Cholesterol			
			Duration of Diabetes to Jan 1, 1937	Highest Fasting Blood Sugar Value, %		Date Started	Date Stopped	Upper Border Cm	Lower Border, Degrees Cm	Long Angle, Diameter, Cm	9th Thoracic Vertebra to Sacrum, Cm	Body Width, Cm	Inter spinal Diameter, Cm	Total, Free, Ester, Mg per 100 Cc					
														Date		Date	per 100 Cc	Mg Ester, % of Total	
I Betaine Taken Regularly (7 Cases)																			
7	F	20 8	13 1	0 47	52	February 1936	September 1937	+2 6 +1 0 +3 9 +5 5	62 60 60 60	19 0 19 0	34 5 31			2/29/36 3/31/36	212 231	50 57	156 166	76 75	
30	M	15 8	11 6	0 55	76	July 1935	March 1936	8+ 7 8	+0 5 +2 0 +3 2	70 62	22 2 22 4 23 5	27 3 30 7 29 8	20 8 23 3 23 0	No change	7/15/35 10/18/35 12/7/35 3/7/36	228 410 220 213	85 104 162 155	143 306 162 158	63 74 73 74
31	F	14 9	8 4	0 49	52	July 1935	March 1936	7+ 7 7	-3 1 -1 5 -1 0	55 53 51	20 3 21 7 22 1	26 0 28 7 27 5	21 4 24 25 2	Slight decrease	7/10/35 11/27/35 12/28/35	269 234 235	76 70 66	193 161 168	71 70 72
32	M	18 2	8 5	0 23	60	July 1935	March 1936	7 7 6+	+2 6 +1 0 +1 1 +5 9	55 50 47	20 8 22 2 22 3 22 9	28 7 29 0 29 7	21 5 21 8 21 8 25 5	Slight decrease	7/15/35 12/7/35 1/4/36 2/1/36	240 156 151 139	69 38 39 38	162 114 109 99	71 76 74 73
37	F	16 4	10 0	0 44	64	July 1935	March 1936	6+ 7	+3 0 +1 5	55 51	21 1 21 5	27 8 28 8	21 6 22 3	No change	8/3/35 8/6/35 10/19/35	281 240 323	68 70 88	205 168 237	76 71 76
39	F	15 5	11 6	0 44	52	April 1935	March 1936	8 9 7	+1 +3 8 +6 3 +8 9	57 53 51 35	22 2 23 7 21 0 21 5	26 7 28 4 29 0 28 1	21 2 26 1 26 1 26 0	Marked decrease	4/8/35 7/19/35 10/16/35 11/16/35 1/11/36	271 235 239 214 226	63 63 59 64 66	200 169 178 166 160	77 72 76 74 71

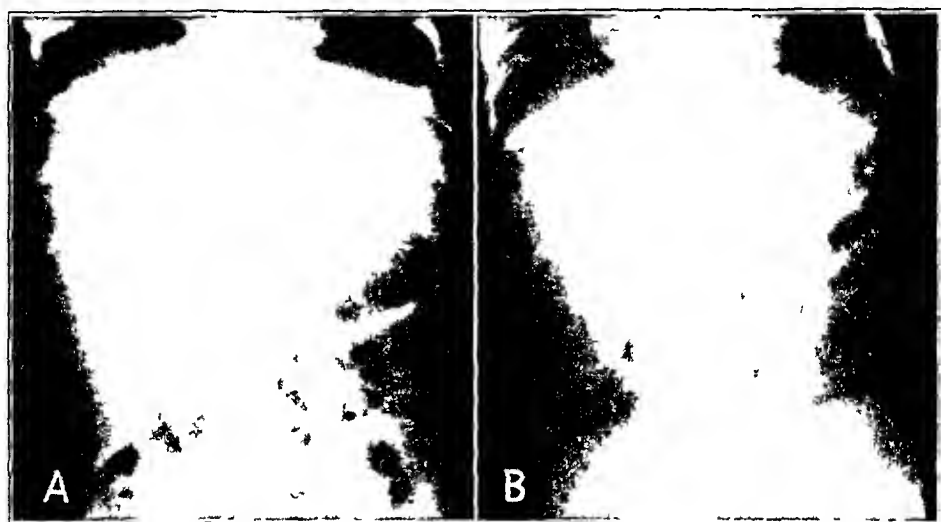
36 F	17.5	6.3	0.30	70	July 1935	March 1936	12/11/35 3/11/36	9 9	+2.5 +2.0	50 50	24.8 25.0	25.5 26.1	28.4 29.3	27.2	No change	8/ 3/35 12/ 7/35 1/ 1/36 3/ 7/36	234 228 212 159	61 71 65 17	165 157 147 112	74 69 69 70
II Betaine Taken Irregularly (5 Cases)																				
11 M	11.8	12.1	0.12	62	March 1935	March 1936	3/25/35 7/20/36	7 7	-2.4 +0.6	48 53	25.3	20.8 22.7	28.5 29.1	22 23.7	Moderate decrease	3/ 6/35 6/20/35	192 190	50	112	74
20 M	13.1	7.8	0.18	34	July 1935	March 1936	4/13/35 1/23/36 3/25/36 7/30/36	8 7+ 8	-2.1 -1.6 -1.4 -1.8	63 58 60 60	24.8 25.5 25.0	21.0 22.2 22.3	28.0 29.2 29.7 28.7	23 24.4 25.0 21.8	No change	7/12/35 9/ 3/35 10/24/35 1/25/36	166 173 142 160	11 26 11	132 107 116	76 75 72
25 M	15.9	6.9	0.12	69	February† 1935	March 1936	2/ 8/35 5/11/35 1/25/36	9+ 8+	-2.3 -3.2 -4.6	54 45 52	30.7+	23.7 23.8 25.7	27.8 35	26.0 27.0 29.5	Moderate increase	3/23/35 4/13/35 10/26/35 1/25/36	178 162 151 215	51 73 59 55	118 107 96 153	71 67 61 74
33 M	14.9	8.5	0.17	56	July 1935	March 1936	3/12/35 5/28/35 12/20/35 3/30/36 7/30/36	7 8+ 8 8	+1.0 +1.1 +0.7 +1.3 +1.7	55 55 55 53	21.5 21.4 22.5 24.0 21.0	21.5 21.4 22.5 23.0 22.8	28.3 28.5 29.8 30.8 29.7	22.3 23.2 24.0 24.3 21.2	Slight decrease	7/12/35 10/26/35 1/11/36 1/25/36 3/30/36	144 201 176 160 136	95 59 47 13 11	95 145 129 113 92	66 71 73 73 70
40 M	14.1	3.6	0.21	32	July 1935	March 1936	4/22/35 10/26/35 7/22/36	8+ 8- 8-	+1.5 +2.1 +5	46 47 48	21.0 18.3	21.1 23.0	28.5 29.0 28.7	23.5 24.5 21.7	Moderate decrease	10/26/35	239	61	166	73

* The daily dose of betaine hydrochloride was 3 Gm. All the observations were made before the institution of treatment with protamine insulin.

† In tables 2 to 4 the values for the size of the liver represent measurements made of roentgenograms as follows: (1) the upper border (the figures given indicate the dorsal vertebra coinciding with the upper margin of the liver, a plus sign indicating the lower margin of the vertebra, a minus sign the upper margin and no sign the midpoint), (2) lower border—centimeters above or below the iliac crest, (3) the angle of the lower tip, (4) the long diameter—the longest straight line measurement from the upper margin to the tip, (5) from the ninth thoracic vertebra to the sacrum—the distance from the lower margin of the ninth thoracic vertebra to the upper margin of the sacrum, (6) the width of the patient's body measured between the inner margins of the ninth ribs at their widest curve, and (7) the interspinal diameter—the distance between the anterior superior spines of the ilia. The last three values are included to indicate the relative sizes of the patient at the various times that the roentgenograms were made.

† 1.5 Gm. daily

(c) *Protamine Insulin*—The use of protamine insulin was begun in this clinic in August 1935 and has been steadily extended. As patients have returned to the hospital for "check-up" they have been shifted to the new preparation, and almost all have continued its use at home. A general summary of the results obtained in the first 1,250 patients has already been published.⁴ Of the children discussed in the present paper, all but 1 are now taking protamine zinc insulin (data concerning the control series and those receiving betaine were collected before the use of protamine insulin was begun). Because of the report by Hanssen,⁵ we watched this group carefully to detect any change in hepatic size.



Roentgenograms of the abdomen in case 41. *A* was taken on July 27, 1936, when treatment with protamine zinc insulin was begun. *B* was taken on September 12, and shows the marked decrease in the size of the liver.

In 19 instances serial examinations were made by roentgenogram. The results in these few cases are presented in table 4. It can be readily seen that concomitant with the use of protamine insulin, there occurred a diminution in the size of the liver in 15, or 78.9 per cent, of the 19 cases. Our impression is that the decrease in size may begin within two weeks after the institution of such therapy, provided this is done under conditions which allow careful dietary regulation and good control of the diabetes.

Less detailed clinical study of other patients by means of physical examination bears out this finding, namely, that with the better control

4 Joslin, E. P. Protamine Insulin, *J. A. M. A.* **109**:497 (Aug. 14) 1937.

5 Hanssen, P. Enlargement of the Liver in Diabetes Mellitus, *J. A. M. A.* **106**:914 (March 14) 1936.

TABLE 3—Control Series *

TABLE 3—Control Series *																			
Case No	Sex	Age on Jan 1, 1937	Duration of Diabetes to Jan 1, 1937	Severity of Diabetes	Highest Fasting Blood Sugar to Jan 1, 1937, %	Usual Daily Dose of Insulin Units	Size of Liver					Summary of Results	Plasma Cholesterol						
							Upper Border	Lower Border	Angle, Degrees	Long Diameter, Cm	9th Thoracic Vertebra to Sacrum, Cm		Body Width, Cm	Inter spinal Diameter, Cm	Date	Total, Free, Ester, Mg per 100 Cc	per 100 Cc	per 100 Cc	of Total
17	M	17.9	9.5	0.29	76		S—	+2.0 +1.7	65 65	21.2 22.2	28.3 30.0	26.5 26.5	1/ 9/35 12/31/35	186 239 185 230	51 69 62 64	137 170 123 166	73 71 67 72		
18	F	16.7	8.8	0.50	30		S+	-1.7 -1.8	90 85	27.7 27.2	22.7 22.6	29.0 29.2	25.0 25.0	No change	11/ 9/35 12/28/35 3/ 7/36	186 239 185 230	51 69 62 64	137 170 123 166	
24	M	13.1	7.0	0.36	18		S	0.0 -1.1	52	22.5 22.5	18.1 19.8	26.7 26.5	21.5 22.7	No change					
61	M	8.7	6.9	0.16	10		S	+7.2 +1.1	60 50	17.5 17.5	19.0 19.5	25.0 24.1	19.5 19.5	Slight decrease					
28	M	13.3	9.8	0.30	21		S	-0.4 +1.0 -3.0	56 56 67	25.0 26.5	19.8 20.7 20.6	27.3 27.8 28.0	19.3 20.3 20.7	No change					
35	F	16.8	11.5	0.25	68		S	+5.5 +7.5	73 57		29.2 23.2	29.2 29.6	21.0 26.0	Slight increase	4/21/35 10/ 5/35 11/ 9/35 12/ 7/35	215 227 235 185	75 51 60 57	106 181 183 121	74 76 71 69
														No change	7/ 3/35 10/ 7/35 12/28/35	283 270 186	71 72 59	211 181 127	75 71 68

* These observations were made before the institution of treatment with protamine insulin (except in case 18, treated with regular insulin).

* These observations were made before the institution of treatment with protamine insulin (except in case 18, treatment was begun on Aug 18, 1936, three days before the roentgenogram was taken)

TABLE 4—Effect of Treatment with Protamine Insulin on the Size of the Liver in Nineteen Cases

Case No	Sex	Age on Jan 1, 1937	Duration of Fasting Diabetes on Jan 1, 1937	Highest Blood Sugar Value, %	Protamine Insulin		Size of Liver							Summary of Results	
					Date Started	Dosage, 1937	Date	Upper Border	Lower Border, Angle, Degrees	Long Diam eter, Cm	9th Thoracic Vertebra to Sacrum, Cm	Body Width, Cm	Inter spinal Diam eter, Cm		
5	F	23 3	16 4	0 51	January 1937	50*	7/ 1/35 10/27/37	6+ 7	+0 7 +4 3	60	25 0 23 0	22 0 22 3	30 0 29 3	25 4	Moderate decrease
6	M	14 7	12 8	0 55	July 1936	36 + 48*	12/ 7/35 7/30/36 11/ 6/37	7 8	+3 5 +5 8 +5 8	53 52 53	24 3 23 8	23 5 24 3 26 3	29 5 29 5 31 0	23 3 24 0	Slight decrease
15	F	21 3	8 8	0 41	January 1936	26 + 86*	12/ 4/35 8/11/36 2/ 3/37	6+ 6+ 6+	+4 3 +3 5 +5 6	63 63 60	30 5 23 0	26 0 26 5 26 4	33 6 34 4	30 3	Moderate decrease
16	F	13 5	9 3	0 40	August 1937	10 + 40*	8/12/37 10/13/37	7+ 7+	-0 8 +2 2	57 53	23 0 26 7	25 6 25 8	29 5 29 5	30 0	Moderate decrease
20	M	13 1	7 8	0 48	July 1936	18 + 22*	7/30/36 3/26/37	8 8+	-1 8 +0 5	60 60	25 0 23 0	22 3 22 7	28 7 28 5	24 8	Moderate decrease
24	M	13 1	7 0	0 36	July 1936	2 + 53*	7/24/36 3/ 3/37	7+ 8+	0 0 +2 1	15 55	21 8 20 0	19 6 20 7	26 5 26 8	22 2 23 5	Moderate decrease
25	M	15 9	6 9	0 41	October 1936	20 + 40*	10/31/36 2/ 6/37	8+ 8+	-3 2 -2 0	15 15	29 0 27 2	26 2 26 1	34 0 30 0		Slight decrease
28	M	13 3	9 8	0 30	July 1936	11*	7/24/36 3/ 3/37	7+ 7+	+1 9 1 1 3	61 65	22 6 21 5	20 5 20 8	27 2 27 2	20 3 21 2	Slight decrease
30	M	15 8	11 6	0 55	March 1936	8 - 68*	3/11/36 7/30/36 3/ 3/37	8 9 8+	+3 2 +3 5 +4 1	62 55 55	21 5 20 0 20 0	23 5 23 8 25 8	29 8 29 4 28 8	23 0 23 3 24 5	Moderate decrease

62	T	160	116	0 12	August 1936	51*	6/8/36 10/24/36 6/11/37	9 10 10+	+13 +03 +20	58 58 60	238 235 230	255 255 265	296 300 310	237 260	Slight decrease
73	M	110	85	0 17	July 1936	21 + 40*	9/8/36 11/2/36 4/27/37 9/20/37	9+ 8+ 9 8+	-20 +26 +06 +16	52 50 43 47	235 222 250 236	226 232 212 215	298 291 302	255	No change
76	T	175	63	0 30	June 1936	70*	12/23/36 3/5/37 9/29/37	8 8+ 8+	+30 +22 +16	13 50 15	260 265 265	267 297 302 315	298 291 302	255	No change
79	M	56	37	0 70	February 1937	26*	2/13/37 7/15/37	6+ 6+	+10 +45	70 60	222 190	188 192	272 212	205	No change
82	T	83	35	0 27	July 1936	16*	7/23/36 10/5/37	8 8+	+20 +08	57 52	182 180	171 186	217 230	182 191	Marked decrease
83	T	78	34	0 44†	June 1936	14 + 30*	7/27/36 9/12/36	8 9	-18 +01	63 53	255 210	215 215	253 217	205 210	No change
85	M	158	60	0 31	July 1936	24*	5/14/36 6/18/36 8/19/36 6/30/37	9 8+ 9 9	-24 00 -10 +12	55 57 195 204 180	175 176 193 193	221 230 222	172 175 180 195	Marked decrease	
82	M	63	03	0 25	October 1936	28 + 42*	7/30/36 7/17/37 10/23/37	7 9 8+	+07 -17 -13	270 270 265	232 260 258	312 312	272 285	Slight decrease	
83	T	97	82	0 43	May 1937	24* 20 + 53*	10/31/36 9/25/37	8+ 7+	+20 +11	45	185 171	183 192	211 232	190 203	No change
						5/28/37 6/4/37 7/16/37 9/22/37	6 6 7+ 7	+15 +20 +26 +18	63 58 38	223 202 203	171 170 171 178	235 212 212 218	175 175 175 180	Slight decrease	
															Moderate decrease

* Protamine Insulin † Not during fasting

Where two figures appear for the dosage, the first one indicates units of regular insulin

of the diabetes that is made possible with protamine insulin, the enlargement of the liver is prevented or alleviated. This suggests that in the diabetic patient the hepatic changes are due not to the lack of some substance present in raw pancreas or its derivatives but to the poor control of the diabetes, with the accompanying disordered fat metabolism. This seems reasonable in view of the fact that if insufficient insulin is given to dogs made diabetic by total pancreatectomy, the liver may become enlarged and fatty and even large amounts of raw pancreas or its derivatives given orally will only partly diminish its size. This form of hepatomegaly obviously is due primarily to poor control of the diabetes.

TABLE 5—*Summary Table of Results as Regards the Size of the Liver*

	Total No of Cases	Increase		No Change	Decrease			Decrease in Size, % of Total Cases
		Slight	Mod- erate		Marked	Mod- erate	Slight	
Control series	6	1		4			1	16.6
Betaine								
Taken regularly	7	1		3	1		2	
Taken irregularly	5		1	1		2	1	50.0
Protamine insulin	19			1	2	7	6	78.9

COMMENT

The trial of raw pancreas or betaine for diabetic children with hepatomegaly has its rationale in the fact, established shortly after the discovery of insulin, that although a completely depancreatized dog can be kept alive for as long as eight months with lean beef, cane sugar and insulin, it eventually dies with signs of hepatic failure unless fresh raw pancreas is added to the diet. In animals not given raw pancreas, postmortem examination reveals enlargement and fatty degeneration of the liver.⁶ Later Hershey⁷ and Hershey and Soskin⁸ concluded that lecithin is the effective constituent of raw pancreas. The problem was carried a step further by Best and his associates,⁹ who established that

6 Allan, F. N., Bowie, D. J., Macleod, J. J. R., and Robinson, W. L. Behavior of Depancreatized Dogs Kept Alive with Insulin, *Brit J Exper Path* 5:75 (April) 1924.

7 Hershey, J. M. Substitution of Lecithin for Raw Pancreas in the Diet of the Depancreatized Dog, *Am J Physiol* 93:657 (June) 1930.

8 Hershey, J. M., and Soskin, S. Substitution of Lecithin for Raw Pancreas in the Diet of the Depancreatized Dog, *Am J Physiol* 98:74 (Aug.) 1931.

9 (a) Best, C. H., Ferguson, G. C., and Hershey, J. M. Choline and Liver Fat in Diabetic Dogs, *J Physiol* 79:94 (July 28) 1933. (b) Best, C. H. The Role of the Liver in the Metabolism of Carbohydrate and Fat. Deposition of Liver Fat, *Lancet* 1:1274 (June 16) 1934.

choline is the component of lecithin which is active in this connection. Furthermore, betaine, an oxidation product of choline, also was found to be effective¹⁰. Accordingly, it seemed reasonable that raw pancreas or betaine might be of use in the treatment of diabetic children with enlargement of the liver.

It is evident from the data which have been presented that although greater or less decrease in size of the liver was seen in 50 per cent of the patients given betaine, the change was not uniformly obtained nor was it usually striking in degree. Certainly some of the results seen must be ascribed to better control of the diabetic condition (with diet and insulin) during the period of administration of betaine. The fact that as good or better results were obtained in the patients who took betaine irregularly, as compared with those who took it regularly, strengthens the belief that the beneficial action was not due wholly to betaine. This lack of specific action may be ascribed to the following factors:

- 1 Choline is found in many foods¹¹ and, as far as we can judge, was already present in adequate amount in the diets of the children.

- 2 Influences other than the lack of choline may well be and probably are the cause of the enlargement of the liver seen in diabetic children. Other factors which Best and his associates have found to possess a lipotropic action are certain dietary proteins¹² and extracts of the anterior lobe of the pituitary gland.¹³ The beneficial effect which followed the use of protamine insulin in our patients suggests that in them uncontrolled diabetes per se was the fundamental cause of the hepatomegaly.

- 3 There is a decided difference between depancreatized dogs with an enlarged, fatty liver and diabetic children with the same complication. In the first place, in the animals, as Chaikoff and his associates¹⁴ have shown, the lipid content of the blood is low. The blood cholesterol value is low, with almost complete disappearance of the ester fraction. In diabetic patients the blood fat and cholesterol values are usually moderately elevated. In almost every case there is a normal percentage of ester cholesterol, and those few values which are reduced are only slightly so. Furthermore, in animals the giving of raw pancreas, with a reduction in the size of the liver, causes a rise in blood fat and

10 Best, C. H., and Huntsman, M. E. The Effects of the Components of Lecithin upon Deposition of Fat in the Liver, *J. Physiol.* **75** 405 (Aug. 10) 1932.

11 Fletcher, J. P., Best, C. H., and Solandt, O. M. Distribution of Choline, *Biochem. J.* **29** 2278 (Oct.) 1935.

12 Best, C. H., Grant, R., and Ridout, J. H. The "Lipotropic" Effect of Dietary Protein, *J. Physiol.* **86** 337 (May 4) 1936.

13 Best, C. H., and Campbell, J. Anterior Pituitary Extracts and Liver Fat, *J. Physiol.* **86** 190 (Feb. 8) 1936.

14 Chaikoff, I. L., and Kaplan, A. The Blood Lipids in Completely Depancreatized Dogs Maintained with Insulin, *J. Biol. Chem.* **106** 267 (Aug.) 1934.

cholesterol values, together with a rise in the ester cholesterol value¹⁵. In our diabetic children receiving betaine this did not occur except to a slight extent in 3 cases (cases 7, 30 and 33) and, in general, one finds a decrease rather than an increase in the blood cholesterol value as the diabetes is brought under better control. In the depancreatized dog with enlargement of the liver due to a lack of choline or lecithin, the giving of choline produces along with improvement in the general condition a paradoxical increase in the sugar content of the urine. In the diabetic patient clinical improvement goes hand in hand with reduction of the glycosuria.

It must be remembered that in the diabetic patient the external secretion of the pancreas, although probably impaired in some cases, is by no means entirely lacking, as it is in the depancreatized dog.

4 The possibility exists that to a greater or less extent the hepatomegaly seen in diabetic children may be due to the accumulation of substances other than fat. In the preceding paper we¹ have presented evidence suggesting that glycogen is not primarily responsible and have suggested the possibility that part of the enlargement in some cases may be due to the imbibition of water incident to hydropic degeneration of the hepatic cells.

There has been considerable discussion as to whether or not choline is the constituent of raw pancreas which is responsible for the beneficial effects seen when raw pancreas is fed regularly to the completely depancreatized dog maintained with insulin. Thus, Ralli, Flaum and Banta¹⁶ reported that lecithin was not as effective as raw pancreas in preventing the deposition of fat in the liver of depancreatized dogs. Then Chaikoff and Kaplan¹⁷ found that choline fed to depancreatized dogs was relatively ineffective in influencing the blood cholesterol value as compared with raw pancreas given in amounts containing far less choline (as calculated from the lecithin content). They concluded that the blood lipid factor is not choline. In studies subsequently reported, these workers¹⁸ stated that whereas choline fed to completely depan-

15 Chaikoff, I. L., and Kaplan, A. The Influence of the Ingestion of Raw Pancreas upon the Blood Lipids of Completely Depancreatized Dogs Maintained with Insulin, *J Biol Chem* **112** 155 (Dec) 1935

16 Ralli, E. P., Flaum, G., and Banta, R. The Results of Feeding Lecithin and Pancreas in Depancreatized Dogs on the Liver Fat and Its Saponifiable and Unsaponifiable Fractions, *Am J Physiol* **110** 545 (Jan) 1935

17 Chaikoff, I. L., and Kaplan, A. Comparative Effects of Pancreas and Choline on Blood Cholesterol of Depancreatized Dog Maintained with Insulin, *Proc Soc Exper Biol & Med* **34** 413 (May) 1936

18 Kaplan, A., and Chaikoff, I. L. The Effect of Choline on the Lipid Metabolism of Blood and Liver in the Completely Depancreatized Dog Maintained with Insulin, *J Biol Chem* **120** 647 (Sept) 1937

creatized dogs in large amounts influences the deposition of fat in the liver, its curative action is slow and daily feeding for a long time is required to produce measurable effects on the liver in which a large amount of fat has accumulated. Furthermore, Prohaska, Dragstedt and Harms¹⁹ have stated that the beneficial effect of raw pancreas in preventing or relieving the fatty changes in the liver cannot be accounted for on the basis of its lecithin or choline content, since the amount of these substances required is relatively great. While agreeing with the conclusion just cited, Kaplan and Chaikoff,¹⁸ criticized the methods used by Dragstedt, Prohaska and Harms. The last named workers²⁰ reported that they had obtained in alcoholic extracts of beef pancreas a substance which they had named lipocaic, which when fed to pancreatectomized dogs maintained with insulin acted in a specific manner to allow survival and to prevent and relieve the deposition of fat in the liver. Results obtained with lipocaic in human beings will be of interest, so far only one report has come to our attention, that of Grayzel and Radwin,²¹ who stated that they obtained a decrease in the size of the liver in 3 diabetic children with the giving of lipocaic, whereas careful control of the diet and adequate insulin treatment had previously been unsuccessful. In their preliminary communication no specific values for the size of the liver before or after treatment were given.

Best²² said he considered that the lipotropic action of raw pancreas may be due to any or all of the following factors: (1) its choline content, (2) its protein content,¹² (3) its enzyme content, allowing for digestion of dietary protein and incidentally for the release of choline from such, and (4) possibly the presence in it of betaine and other substances closely related to choline.^{9b} An influence due to pancreatic juice has been denied by Prohaska, Dragstedt and Harms.¹⁹

Relevant to this discussion is the recent paper of Aylward and Holt.²³ These investigators found no evidence of the presence of a lipotropic factor in pancreas other than choline. Their work was with normal rats rather than depancreatized dogs, however.

19 Prohaska, J. V., Dragstedt, L. R., and Harms, H. P. The Relation of Pancreatic Juice to the Fatty Infiltration and Degeneration of the Liver in the Depancreatized Dog, *Am J Physiol* **117** 166 (Sept.) 1936.

20 Dragstedt, L. R., Prohaska, J. V., and Harms, H. P. Observations on a Substance (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, *Am J Physiol* **117** 175 (Sept.) 1936.

21 Grayzel, H. G., and Radwin, L. S. Treatment of Hepatomegaly in Juvenile Diabetes Mellitus with a Pancreatic Extract, *Proc Soc Exper Biol & Med* **37** 724 (Jan.) 1938.

22 Best, C. H. Personal communication to the author, footnotes 9 to 13.

23 Aylward, F. X., and Holt, L. E., Jr. The Nature of the Lipotropic Agent in Pancreas, *J Biol Chem* **121** 61 (Oct.) 1937.

SUMMARY

The effect of raw pancreas on hepatomegaly was observed in 2 diabetic children, that of betaine hydrochloride in 12 and that of protamine insulin in 19

No significant change in the size of the liver was observed concomitant with the use of raw pancreas. With the use of betaine a greater or less diminution was seen in 50 per cent of the 12 patients, and with the use of protamine insulin it was seen in 15, or 78.9 per cent, of the 19 patients. Some diminution in size was observed in 1 of 6 patients in a control series.

The beneficial effect seen with the use of protamine insulin is ascribed to the better control of the diabetic condition.

It is concluded that enlargement of the liver in diabetic children is due in the average case chiefly to poor control of the diabetes and not to a lack of choline or of some other agent derived from raw pancreas.

STUDY OF THE DERANGED CARBOHYDRATE METABOLISM IN CHRONIC INFECTIOUS HEPATITIS

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Hypoglycemia has been the outstanding and most constant result of the disturbed carbohydrate metabolism observed when severe injury of the liver has been found clinically or produced experimentally. It appears to have been established that in the normal organism the presence of the liver is necessary for the maintenance of a normal glycemic level¹. It has been shown that the liver has at least three separate functions directly concerned with the metabolism of dextrose. These functions are (1) glycogenesis, (2) glycogenolysis and (3) the production of dextrose and the deposition of glycogen from noncarbohydrate precursors (glycogenic amino acids and glycerol fraction of fats). The balance between glycogenesis and glycogenolysis allows the liver to function as a storehouse of readily available dextrose to be delivered into the blood stream in times of need.

From these facts it is apparent that there are several possible explanations for the hypoglycemia observed in cases of severe hepatic injury. That the mechanism is not necessarily analogous to partial or complete removal of the liver is obvious. If glycogenesis alone were impaired, the hypoglycemia noted during fasting could be due to insufficient storage of glycogen in the liver, even though the glycogenolytic function was normal. On the other hand, impaired conversion of glycogen to dextrose (glycogenolysis) could account for hypoglycemia without involving the glycogenic mechanism. This would result in the retention of an abnormally large amount of glycogen in the liver. In the well fed organism it seems unlikely that the hypo-

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1 Mann, F C, and McGath, T B. The Effect of Removal of the Liver on the Blood Sugar Level, Arch Int Med 30 73 (July) 1922

glycemia could be explained wholly on the basis of an inability to produce dextrose from noncarbohydrate precursors, since this source yields only a small fraction of the total dextrose of the metabolic mixture. That the simultaneous impairment of two or all of these functions could result in hypoglycemia can be conceded.

Another line of reasoning must not be ignored. It might be argued, purely hypothetically, that the hypoglycemia is the result of increased oxidation of dextrose attending severe hepatic lesions. In support of this conception could be presented those cases of diabetes mellitus reported in the literature² in which remarkable improvement or even "cure" has been shown with the development and progression of cirrhosis of the liver. But the literature is devoid of respiratory data to support or refute such a hypothesis. The conclusions have been drawn on the basis of blood sugar levels and glycosuria. Respiratory data, among other factors which preclude such a hypothesis, will be given presently.

It has been demonstrated by Underhill,³ Bodansky,⁴ Izume and Lewis,⁵ McIntosh,⁶ Cross and Blackford⁷ and others that hepatotoxic chemicals such as hydrazine, phosphorus, chloroform, neoarsphenamine and carbon tetrachloride may produce hypoglycemia. Izume and Lewis,⁵ using rabbits, showed that in hydrazine poisoning the function of hepatic glycogenesis was impaired. These animals exhibited low blood sugar levels during fasting. After the administration of dextrose the glycogen content of the liver was lower than that of the control animals, and the blood sugar level was higher, indicating an inability of the liver to remove dextrose from the blood stream and to deposit it as glycogen. It was found that the ability of the liver to deposit glycogen after the administration of glycogenic amino acids was also impaired.

2 Bordley, J, III. Disappearance of Diabetes Mellitus During Development of Cirrhosis of the Liver, *Bull Johns Hopkins Hosp* **47** 113, 1930. Cirrhosis of the Liver, Cabot Case 22261, *New England J Med* **214** 1314, 1936. Strieck, F. Diabetes und Lebercirrhose, *Deutsches Arch f klin Med* **178** 167, 1936.

3 Underhill, F P. Influence of Hydrazine upon the Organism, with Special Reference to the Blood Sugar Level, *J Biol Chem* **10** 159, 1911.

4 Bodansky, M. Production of Hypoglycemia in Experimental Derangement of the Liver, *Am J Physiol* **66** 375, 1923, Effect of Chloroform and Phosphorus Poisoning on Carbohydrate Tolerance, *J Biol Chem* **58** 515, 1923.

5 Izume, S, and Lewis, H B. The Influence of Hydrazine and Its Derivatives on Metabolism. II. Changes in the Non-Protein Nitrogenous Constituents of the Blood and in the Metabolism of Injected Glycine in Hydrazine Intoxication, *J Biol Chem* **71** 33, 1926. Lewis, H B, and Izume, S. The Influence of Hydrazine and Its Derivatives on Metabolism. III. The Mechanism of Hydrazine Hypoglycemia, *ibid* **71** 51, 1926.

6 McIntosh, R. Acute Phosphorus Poisoning, *Am J Dis Child* **34** 595 (Oct.) 1927.

7 Cross, J B, and Blackford, L M. Fatal Hepatogenic Hypoglycemia Following Neoarsphenamine, *J A M A* **94** 1739 (May 31) 1930.

Von Gierke's disease illustrates a type of hepatogenic hypoglycemia the mechanism of which appears to be wholly on the basis of disturbed glycogenolysis. In this disease of childhood, evidenced by hypoglycemia and hepatic enlargement, the liver is found to contain a great excess of glycogen, indicating no disability in its deposition. Thus, an abnormally high glycogen content of the liver associated with chronic hypoglycemia has been interpreted as being due to a deficient glycogenolytic mechanism. Some have attributed this disturbance to a lack or deficiency of an enzyme necessary for the conversion of glycogen to dextrose.

All the clinical cases of chronic hepatogenic hypoglycemia reported have been associated with marked diffuse destructive or degenerative lesions of the liver. In the cases reported by Nadler and Wolfer⁸ and by Crawford⁹ a primary neoplasm involved most of the hepatic tissue. In those of Josephs¹⁰ and of Judd, Kepler and Rynearson¹¹ there was severe fatty degeneration of the liver. The case reported by Blackford⁷ was due to marked toxic hepatitis following neoarsphenamine therapy. In the case reported by Moore, O'Farrell and Headon¹² there was subacute degenerative hepatitis of unknown etiology. Metabolic studies in clinical cases of this disturbance are few.

The present report consists of detailed studies of 6 patients with chronic hypoglycemia of hepatic origin. Case 1, the metabolic studies of which were continued for over a year, is unique in several ways. The hypoglycemia had been of three years' duration at least. It was shown to be due to ascending infectious hepatitis, the result of chronic purulent cholecystitis. In this case there was remarkable recovery of the disturbed carbohydrate metabolism after removal of the source of the hepatitis.

CASE 1—W. F., a 47 year old laborer, was first admitted to the University Hospital on May 2, 1935, complaining of attacks of unconsciousness. Since March 1934 he had been having periodic attacks of unconsciousness, which always occurred nine to twelve hours after the evening meal and lasted as long as thirty-six hours. The number of attacks averaged two or three each month, although there had been one period of four months without an attack. The attack was characterized by excessive sweating, vomiting and incontinence of

8 Nadler, W. H., and Wolfer, J. A. Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, *Arch. Int. Med.* **44**: 700 (Nov.) 1929.

9 Crawford, W. H. Hypoglycemia with Coma in a Case of Primary Carcinoma of the Liver, *Am. J. M. Sc.* **181**: 496, 1931.

10 Josephs, H. Spontaneous Hypoglycemia in Childhood, *Am. J. Dis. Child.* **38**: 746 (Oct.) 1929.

11 Judd, E. S., Kepler, E. J., and Rynearson, E. H. Spontaneous Hypoglycemia. Two Cases with Fatty Metamorphosis of the Liver, *Am. J. Surg.* **24**: 345, 1934.

12 Moore, H., O'Farrell, W. R., and Headon, M. F. Spontaneous Hypoglycemia Associated with Hepatitis, *Brit. M. J.* **1**: 225, 1934.

urine and feces. There were no convulsions. The attack would end gradually, but the patient would remain disoriented for many hours. He would have no memory of the entire incident. There had been a gradual reduction in weight, from 154 to 130 pounds (from 70 to 59 Kg), in three years. There were no other complaints.

In 1924 a ruptured colonic diverticulum was repaired, in 1932 subtotal thyroidectomy was performed for nontoxic goiter. There had never been symptoms referable to either the gallbladder or the liver.

Physical, neurologic and laboratory examinations revealed no abnormalities except mild secondary anemia. On discharge no etiologic diagnosis was made.

He returned on Jan 6, 1936, stating that his attacks had continued at about the same rate. The local physician suggested the presence of an intracranial lesion, since on one occasion an attack had been quickly terminated by the use of 50 per cent solution of dextrose intravenously.

The physical examination again showed no significant abnormality. The urine was normal. The Kahn test gave a negative reaction. Examination of the blood showed macrocytosis of the red blood cells, a color index of more than 1 and a normal amount of hemoglobin. Roentgenograms of the skull showed no abnormality. Several spinal punctures showed normal spinal fluid under normal pressure. The basal metabolic rates were found to be -13 per cent and -3 per cent, respectively, on two occasions. A cholecystogram showed slight visualization of the gallbladder, with possible stone. The bilirubin value was 2.5 mg per thousand cubic centimeters of blood.

At this point our metabolic studies were begun. A respiration chamber¹³ employing the principle of continuous indirect calorimetry by the open circuit method was used to obtain respiratory data. Frequent checks with alcohol demonstrated that the method was capable of determining over 99 per cent of the gaseous exchange. Blood sugar values were determined by the Benedict¹⁴ method and urinary nitrogen values by the Kjeldahl method. Serum protein values were determined by the micro-Kjeldahl method, direct nesslerization being employed and appropriate correction being made for nonprotein nitrogen.¹⁵

The patient was kept in bed and given a diet extremely low in carbohydrate (1,600 calories, 17 Gm of carbohydrate and 50 Gm of available dextrose). The following morning and for five successive mornings he was found to be disoriented and semicomatose or totally unconscious. The blood sugar values during fasting ranged from 14 to 18 mg per hundred cubic centimeters. Rapid relief was obtained by the administration of dextrose intravenously.

The following groups of laboratory studies, the numerical data of which will be seen in the accompanying charts, seemed to indicate that the hypoglycemia was on the basis of impaired hepatic function.

13 Newburgh, L. H., Johnston, M. W., Wiley, F. H., Sheldon, J. M., and Murrill, W. A. A Respiration Chamber for Use with Human Subjects, *J Nutrition* **13** 193, 1937.

14 Benedict, S. R. The Analysis of Whole Blood. II. The Determination of Sugar and of Saccharoids (Non-Fermentable, Copper-Reducing Substances), *J Biol Chem* **92** 141, 1931.

15 Campbell, W. R., and Hanna, M. I. Short Method for Determining Albumin-Globulin Ratios in Human Serum, *Tr Roy Soc Canada (Sect V, Biol sc)* **25** 29, 1931. Wu, H. New Colorimetric Method for Determination of Plasma Proteins, *J Biol Chem* **51** 33, 1922. Koch, F. C., and McMeekin, T. L. A New Direct Nesslerization Micro-Kjeldahl Method and a Modification of the Nessler-Folin Reagent for Ammonia, *J Am Chem Soc* **46** 2066, 1924.

1 Dextrose tolerance tests showed an impaired ability to remove absorbed dextrose from the blood stream in the normal length of time. This led to a high delayed plateau curve similar to that seen in the diabetic state. The blood sugar levels during fasting, however, at the beginning of the tests were abnormally low. Such curves can be produced experimentally by hepatic injury¹⁶

2 Respiratory data indicated that the oxidation of dextrose was normal both in the fasting state and after the ingestion of dextrose. This demonstrated that the delay in removing absorbed dextrose from the blood stream was due not to decreased oxidation of dextrose but to impaired glycogenesis. Further, these data indicated that the low blood sugar levels of the fasting state were not accompanied by increased oxidation of dextrose, as would be expected in hyperinsulinism¹⁷. Together these observations suggested that the low blood sugar levels of the fasting state were brought about by impaired glycogenesis and perhaps impaired glycogenolysis.

3 Bromsulphalein excretion tests showed retention of 90 and 70 per cent of the dye (bilirubin, 2.5 mg per thousand cubic centimeters of blood).

4 Total serum protein values were abnormally low, with inversion of the albumin-globulin ratio.

5 Macrocytosis of the red blood cells was marked.

6 Galactose tolerance was impaired.

Before comparing the preoperative and the postoperative data we shall describe the data relative to the operative treatment. Exploratory laparotomy was done on March 9 by Dr. F. A. Collier. The pancreas was carefully examined and was found to be grossly normal. The liver was of normal size but abnormally pale. Its entire surface was granular, with nodules about 2 mm in diameter. The gallbladder was distended and contained several large stones and 2 or 3 ounces (60 to 90 cc.) of thick yellow pus. The gallbladder was removed, and a specimen of the liver was taken for biopsy. The pathologist reported evidence of cholelithiasis. A large, soft, pigmented calculus appeared to be made up almost entirely of inspissated bile pigment. There was active purulent cholecystitis with areas of ulceration. Granulation tissue was present in the wall of the gallbladder. The pigment masses in the lumen were of the same nature as those seen in the calculus. Biopsy of the liver showed active chronic cholangiolitis, biliary cirrhosis, cloudy swelling and fatty infiltration but no neoplasm. Figure 1 shows a section of the specimen of the liver.

The accompanying charts, comparing the preoperative data with those obtained during a nine month postoperative period, indicate remarkable improvement in the capacity of the liver to deal with dextrose. Simultaneously, the other indications of abnormal hepatic function disappeared.

The accompanying table shows the respiratory metabolism of the patient and that of the control subjects under a variety of conditions. The patient's ability to oxidize dextrose was neither decreased nor increased over the normal either before or after operation. The disturbance, then, could not be said to be one of overoxidation of dextrose.

Figure 2 demonstrates the gradual return of the glycogenic function of the liver in the postoperative period. The absorbed dextrose was then being removed

16 Collier, F. A., and Troost, F. L. Glucose Tolerance and Hepatic Damage, *Ann Surg* **90** 781, 1929. Cross and Blackford.⁷

17 Liu, S. H., Loucks, H. H., Chou, S. K., and Chen, K. C. Adenoma of Islet Cells with Hypoglycemia and Hyperinsulinism. Report of Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of the Tumor, *J Clin Investigation* **15** 249, 1936.

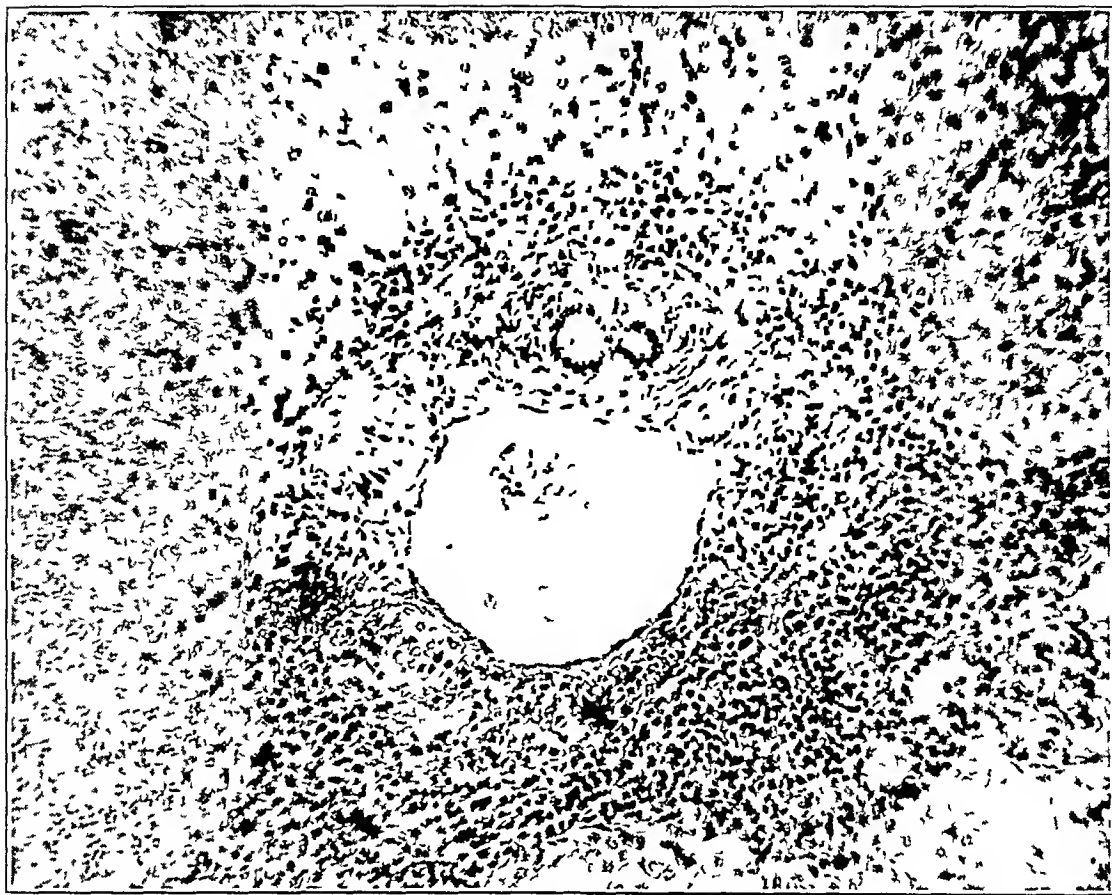


Fig 1 (case 1) —Section of the specimen from the liver removed for biopsy

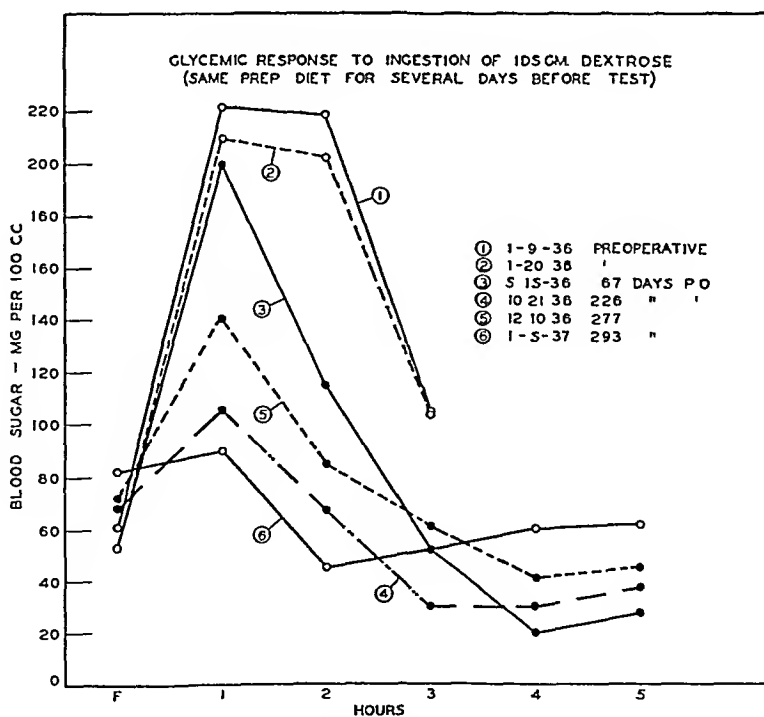


Fig 2 (case 1) —Chart showing the blood sugar values

from the blood stream rapidly. Note that as time went on the level of the blood sugar during fasting rose from 51 to 81 mg per hundred cubic centimeters, the patient having been taking the same diet for several days before each test. Note also that the blood sugar level at the end of the fifth hour showed a progressive rise. These observations indicated gradual improvement in the patient's ability to maintain a blood sugar level closer to the normal. It is apparent, however, that there was still some active disturbance in the function of glycogenolysis. For curve 4, for example, showing rapid removal of dextrose from the blood stream, there must have been an impaired glycogenolytic mechanism which blocked the release of dextrose from the liver even in time of need. The

Carbohydrate Oxidized in Four Hours

Date	Subject	Dietary Preparation (3 Days Before Test)		Dextrose Ingested in Chamber, Gm	Carbon Dioxide Produced, Liters	Oxygen Absorbed, Liters	Urinary Nitrogen, Gm	Dextrose Oxidized in Chamber, Gm
		Calories	Carbo- hydrate, Gm					
2/28/36	Case 1	2,800	150	50	52	61	1.5	36
	Control	2,750	100	50	56	68	2.3	31
	Control	2,750	100	50	51	57	2.4	42
	Control	2,750	200	50	56	63	2.5	44
	Control	2,750	200	50	51	58	1.9	37
4/13/37	Case 2	2,400	200	50	67	79	3.6	39
5/28/36	Case 1	3,000	500	0	61	76	2.0	29
	Control	4,200	500	0	62	75	2.1	33
6/29/36	Case 1	2,600	200	0	59	76	1.9	19
	Control	2,750	200	0	47	59	2.2	16
	Control	2,750	200	0	48	61	2.0	18
7/ 1/36	Case 1	2,600	200	200	67	70	1.9	68
	Control	2,750	200	200	66	68	2.8	65
	Control	2,750	200	200	68	75	1.6	63
7/24/36	Case 3	2,600	100	100	54	61	1.9	45
	Control	2,600	100	100	55	61	2.0	49
1/26/37	Case 6	2,400	200	100	55	58	1.6	54
	Control	2,750	200	100	56	60	2.3	54
	Control	3,000	200	100	59	69	1.7	49
	Control	3,000	200	100	60	67	2.1	52

improvement in glycogenolysis appeared to lag considerably behind that of glycogenesis.

Figure 3 again demonstrates the disturbed glycogenolytic mechanism. Although the ability to maintain a normal blood sugar level during fasting had returned, there was little change in the glycemic response to the injection of epinephrine.

Figure 4 shows the average blood sugar levels during fasting maintained by the patient for progressive periods over the year of study. For each period the daily blood sugar value during fasting was determined to obtain the average for the period. Periods VIII, IX, XI, XII and XIV, all falling in the postoperative period, while the patient was eating a general diet (about 300 Gm of carbohydrate daily), showed a return of the ability to maintain a normal blood sugar level during fasting. Period I, the preoperative period, with a general diet, showed an average fasting level of 58 mg. In periods VI and VII improvement continued, in spite of the fact that the carbohydrate of the daily diet was reduced from

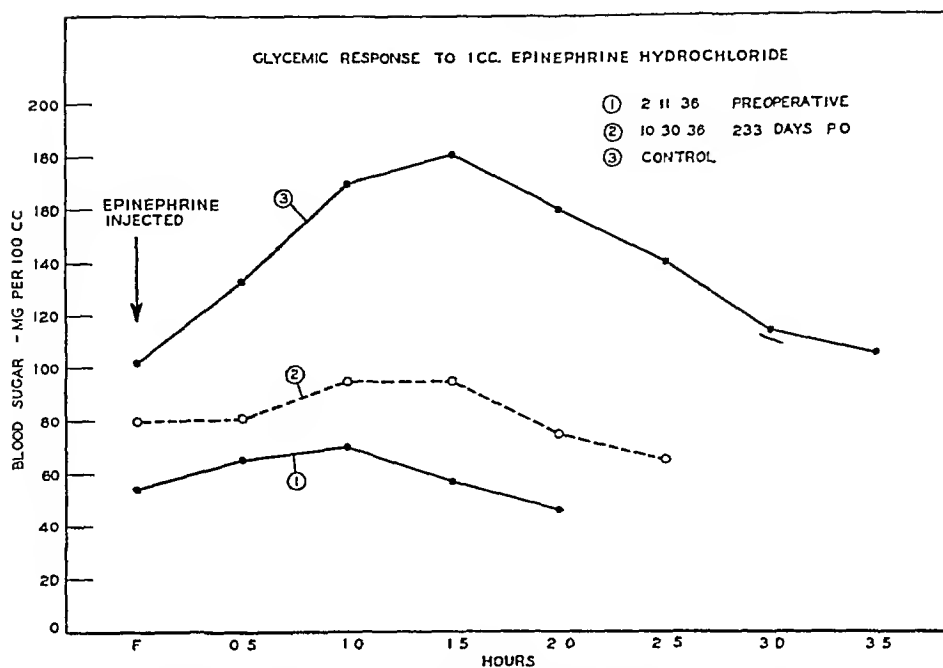


Fig 3 (case 1) —Chart showing the blood sugar values

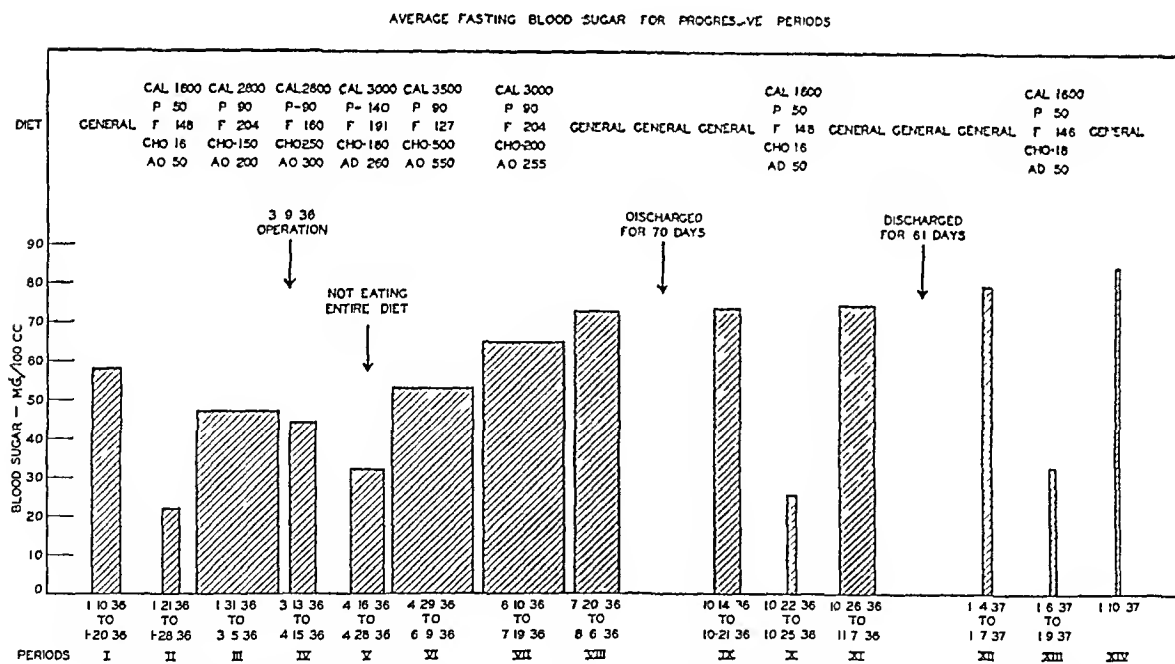


Fig 4 (case 1) —Chart showing the average levels of the blood sugar during fasting for progressive periods

500 to 200 Gm. Periods II, X and XIII represented the response to a sharply restricted intake of carbohydrate. Although unquestioned improvement had taken place in the postoperative period, this appeared to be the most sensitive test of complete recovery. Without this observation there was little to indicate any abnormality in the metabolism of carbohydrate at this stage of recovery. In fact, by this time all the other evidence suggesting abnormal function of the liver had disappeared.

The progressive improvement in the protein level of the blood serum is seen in figure 5. The values for total serum protein returned to their normal level, and the albumin-globulin ratio, which had been inverted, became normal. It should be noted here that the bromsulphalein excretion was normal in the last three determinations. August 7, 15 per cent, October 14, 20 per cent, and December 10, 18 per cent retention of the dye. The last galactose tolerance test,

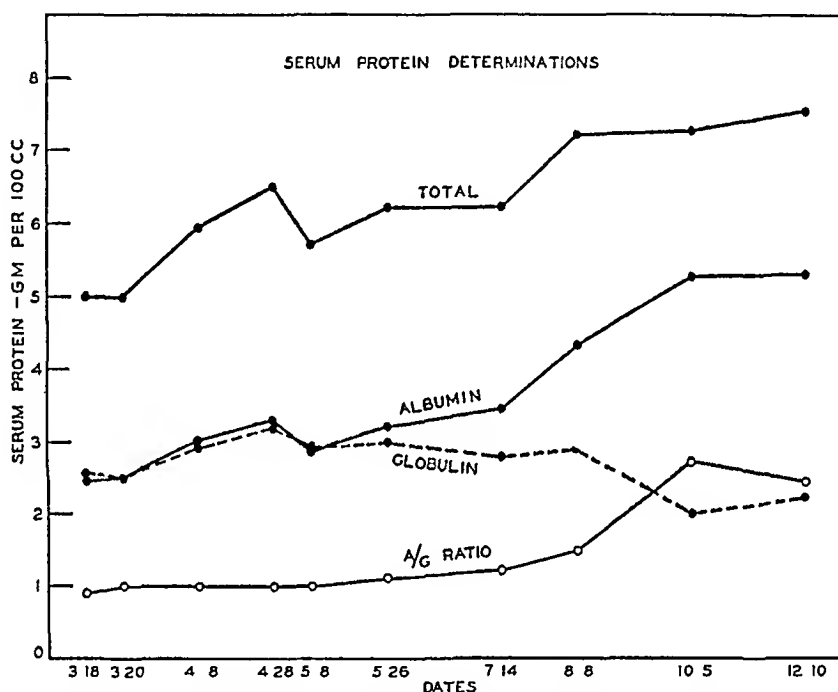


Fig 5 (case 1) —Chart showing the values for blood protein

on October 14, gave a normal result. Macrocytosis of the red blood cells disappeared gradually, and on October 14 the blood was considered normal.

There have been no spontaneous hypoglycemic attacks since operation. Since the completion of these studies the patient has been carrying on his normal activities in apparent good health.

CASE 2—F D, a 55 year old farmer, was admitted to the University Hospital on March 31, 1936. His chief complaints were of swelling of the neck and attacks of unconsciousness. He had been a resident of Michigan all his life and had noted gradual enlargement of the thyroid gland for thirty years. There was nothing to suggest thyrotoxicosis.

For three years there had been attacks of unconsciousness, eight in all, each occurring in the early morning. Each was characterized by premonitory weakness and instability. This was immediately followed by a period of unconsciousness, lasting from a few minutes to several hours. There were no convulsions. Profuse

sweating was associated with the attack. He had found that eating candy would ameliorate or prevent an attack. There had been two such episodes in the past year.

The past history contributed nothing of significance. There had never been symptoms referable to either the liver or the gallbladder.

Physical examination showed a well developed, well nourished middle-aged man who did not appear ill. There was a medium-sized adenomatous goiter. The heart was of borderline size. The chest was otherwise normal. The blood pressure was 170 systolic and 115 diastolic. The liver and spleen were not palpable. There were no other abnormal physical findings.

The urine was normal, and the Kahn test gave a negative reaction. On repeated examinations the red blood cells showed definite macrocytosis, there was a color index above 1 and the hemoglobin content was normal. This suggested hepatic disease to the hematologist. The blood was otherwise normal. A cholecystogram demonstrated complete nonvisualization of the gallbladder. Roentgenograms of the skull showed no evidence of intracranial disease. The basal metabolic rates were +15 per cent and +13 per cent, respectively, on two occasions. The bilirubin content of the blood was 1 mg per thousand cubic centimeters. The bromsulphalein test gave a normal result. The serum protein values were 69 per cent, total protein, 38 per cent, albumin, and 31 per cent, globulin, and the albumin-globulin ratio was 1.2. The results of the dextrose tolerance tests, in milligrams per hundred cubic centimeters, were as follows:

Date	Fasting	Hours			
		1	2	3	4
4/1/36	50	135	202	142	
4/6/36	65	200	242	184	145

The patient was kept in bed and fed a low carbohydrate diet (1,600 calories, 17 Gm of carbohydrate). For the next three successive days the blood sugar values during fasting were 26, 28 and 26 mg per hundred cubic centimeters, respectively. The patient was semicomatose when the blood sugar was at these levels and quickly recovered with the administration of dextrose intravenously.

The respiratory data for this patient are given in the accompanying table. When these data are compared with those for the controls, it is found that the oxidation of dextrose by the patient was normal under the conditions studied.

The patient refused operation and has not been heard from since discharge from the hospital.

Comment—The evidence presented seems to justify the inclusion of this case in the group of cases of hepatogenic hypoglycemia. It appears that the disturbance in carbohydrate metabolism was similar to that described in case 1 and that the hypoglycemia could not be explained on the basis of increased oxidation of dextrose.

CASE 3—W S, a 50 year old laborer, came to the University Hospital on July 8, 1936, complaining of peculiar attacks of disorientation of one year's duration. The attacks would come on at any time of the day or night and recently had been occurring two or three times a week. Consciousness was not completely lost in any of the attacks. There was premonitory blurring of vision, followed by tinnitus, marked apprehension, bobbing of the head from side to side and occasionally involuntary muscular twitching. There were no other complaints.

Since late childhood there had been periodic attacks of jaundice lasting several weeks to two months. This situation occurred about once a year, the longest period of freedom having been four years. During these periods the stools were clay colored, and the urine was dark. There was no associated dyspepsia or abdominal pain.

Twelve years previously he had a primary penile sore, and weekly anti-syphilitic treatments were given for one year.

Physical examination showed a well nourished middle-aged man who did not appear ill. There was faint icterus of the scleras and skin. The pupils reacted sluggishly to light. There was a generalized shotty lymphadenopathy. The chest was normal. The blood pressure was 115 systolic and 80 diastolic. A firm margin of the liver could be felt 3 cm below the right costal margin. The spleen was not palpable. The reflexes were normal.

Laboratory examination showed that the urine was normal. The blood showed marked macrocytosis, a color index above 1 and a normal amount of hemoglobin. The Kahn test of the blood showed a 1 plus reaction. The spinal fluid was normal in all respects. The bilirubin content of the blood was 17 mg per thousand cubic centimeters. The bromsulphalein test showed 80 per cent retention of the dye. The serum protein values were 74 per cent, total protein, 34 per cent, albumin, and 4 per cent, globulin, and the albumin-globulin ratio was 0.8. A cholecystogram demonstrated complete nonvisualization of the gallbladder. The results of the dextrose tolerance tests, in milligrams per hundred cubic centimeters, were as follows:

Date	Fasting	Hours				
		1	2	3	4	4½
7/7/36	78	148	88	32	45	
7/14/36	91	230	184	88	28	32

For three days after the giving of a restricted carbohydrate diet the blood sugar value during fasting was 78, 80 and 53 mg per hundred cubic centimeters, respectively.

The respiratory data for this case are given in the accompanying table.

On August 1 exploratory laparotomy was done. A considerable amount of clear free fluid was present in the abdominal cavity. The liver was considerably enlarged and firm. The surface was diffusely nodular, suggesting cirrhosis. The spleen was not enlarged. The pancreas was firm and indurated. The gallbladder was distended and tense. No stones were felt. The common duct appeared normal. Specimens of the liver and pancreas were taken for biopsy. Cholecystogastrostomy was done with the hope that internal drainage of the biliary sac might be accomplished. Postoperatively the patient went into shock and died, in spite of all supportive measures.

The pathologist gave the following report. The specimen from the liver showed active chronic hepatitis, with active regeneration of the hepatic cells, leading to an early stage of nodular cirrhosis. The hepatic cells were swollen, with marked vacuolation of small groups of cells. The hepatic cells showed a rich but highly variable content of glycogen. Many cells contained sufficient glycogen to result in a deep red staining reaction, while other cells were devoid of stainable carbohydrate. The gallbladder showed chronic cholecystitis with fibrosis of the wall. The specimen from the pancreas contained small but numerous islands. The external secretory portion of the pancreas showed slight

fatty atrophy Examination of the whole organs showed essentially the same picture Careful sectioning revealed no evidence of pancreatic neoplasm

Comment—In this case the pathologic changes were similar to those described in case 1 Both the pathologic changes and the disturbance in carbohydrate metabolism were less severe The patient's ability to store dextrose as glycogen in the liver, although somewhat impaired, appeared to be much less affected than in the 2 preceding cases This was demonstrated by the dextrose tolerance curves and by the presence of a considerable store of glycogen in the liver The function of rapid glycogenolysis seemed to have been impaired and could account for the periodic hypoglycemic episodes It appears evident that the hypoglycemia, which was well established by the fourth hour in both dextrose tolerance curves, could not be explained on the basis of increased oxidation of dextrose in the four hour period (table)

CASE 4—F P, a 66 year old farmer, was admitted to the University Hospital on Sept 9, 1936, in deep coma The history was meager and unreliable, being obtained from relatives About six months before entry he had begun to complain of intermittent pain in the right upper quadrant of the abdomen There had been no obvious jaundice His appetite had been decreasing, and there had been gradual loss of weight for three months Edema of the lower extremities had begun about two months before entry and persisted Extreme weakness had been of two weeks' duration The night before entry he had gradually lapsed into coma There had been no previous periods of unconsciousness The past history was not obtainable

Examination showed a malnourished man of late middle age who was in deep coma There was moderate pallor but no icterus The temperature was 94 F, the pulse rate 68 and the respiratory rate 16 The blood pressure was 100 systolic by palpation The extremities were cold, and the patient was perspiring profusely The pupils reacted normally to light All the tendon reflexes were absent, and no abnormal reflexes were obtained The heart was moderately enlarged The lungs were clear A mass the size of an orange, hard and freely movable, was felt deep in the right upper quadrant of the abdomen The liver and spleen could not be felt There was edema of the lower extremities, extending to the groin and including the genitalia

The urine was normal The blood showed marked secondary anemia, with a hemoglobin value of 38 per cent (Sahl) The Kahn test gave a negative reaction The nonprotein nitrogen content was 29.6 mg per hundred cubic centimeters The carbon dioxide-combining power was 66 volumes per cent The blood sugar value was 14 mg per hundred cubic centimeters

After 100 cc of 50 per cent solution of dextrose was given intravenously the patient became conscious and rational on questioning The temperature, pulse rate and respiratory rate became normal, but the blood pressure remained low A continuous intravenous infusion of 5 per cent solution of dextrose was given until 3 p m the following day The patient remained alert and cooperative At 10 a m the next day profuse sweating occurred, with a rectal temperature of 95 F, and he lapsed into coma The blood sugar value at this time was 20 mg per hundred cubic centimeters Again, a continuous intravenous injection of dextrose was given for the next fifteen hours, with the same dramatic result

Eight hours later the patient was again in coma, with a blood sugar reading of 12 mg per hundred cubic centimeters. Dextrose again helped, but generalized anasarca progressed rapidly, and on September 14 respirations ceased.

Postmortem examination showed marked anasarca and polyserositis. There were terminal hypostatic pneumonia and cardiac dilatation. A large, friable, fungating, mucoid mass, found to be arising from the duodenal mucosa, completely encircled the duodenum. It had grown into the head of the pancreas. The remainder of the pancreas appeared normal. The ampulla of Vater was patent, and bile was present in the duodenum. The common bile duct was greatly dilated, however. The liver was of normal size, and the gallbladder was grossly normal.

Microscopically, the mass was found to be adenocarcinoma mucosum, primary in the region of the ampulla of Vater. The pancreas showed direct extension of the neoplasm into its own substance. The islands of Langerhans were small. There was no evidence of neoplastic pancreatic tissue. The liver showed chronic passive congestion and mild biliary obstruction. There was increased stroma in the islands of Glisson, with lymphocytic proliferation and infiltration in the bile ducts. Staining for fat showed no lipoidosis. The gallbladder revealed thickening and inflammatory infiltrations in its wall, fragments of biliary calculi and chronic cholecystitis.

Comment—Although no respiratory data were obtainable in this case, the pathologic changes indicated that the hypoglycemia was on the basis of hepatic dysfunction. The changes in the gallbladder and liver were similar to those observed in the previous cases.

We believe that the hypoglycemic status was brought to light in this case by the sharply restricted intake of food, which, in turn, was the result of an intestinal neoplasm. The hypoglycemic response was similar to that which we have produced with a restricted diet. It seems probable that the functional hepatic damage was the result of the involvement of the biliary tract. It is noteworthy in this case, as in the previous ones, that the degree of hepatic damage histologically was not extremely marked. The functional capacity, however, as regards carbohydrate metabolism, was greatly affected.

CASE 5—T. F., a 52 year old housewife, was admitted to the University Hospital on Nov. 10, 1937, complaining of jaundice. For about six years she had had symptoms typical of dyspepsia due to disorder of the gallbladder. Three years previously there began to occur true biliary colic associated with transient jaundice. On Oct. 5, 1936, cholecystectomy was done at the Foote Memorial Hospital, in Jackson, Mich. Purulent cholecystitis and cholelithiasis were present at that time. A drainage tube was inserted, and pus and bile continued to drain for seven weeks postoperatively. The wound closed, and the patient felt well again until April 1937, when she noticed the onset of progressive painless jaundice. Nausea, anorexia and lethargy supervened. Clay-colored stools and dark urine became constant. Profuse sweats occurred frequently in the early hours of the morning for a month before entry. There had been no significant loss of weight.

The past history contributed little.

Physical examination revealed a poorly nourished middle-aged woman who appeared chronically ill. There was moderate generalized icterus. The tem-

perature was 102 F, the pulse rate 96 and the respiratory rate 20. The heart and lungs were normal. The blood pressure was 120 systolic and 80 diastolic. The abdomen showed a well healed right rectus excision. The liver was extended about 3 cm below the right costal margin but was not tender. The spleen was not felt. There was no other significant physical finding.

The urine was normal except for the presence of a large amount of bile. The stools were acholic. Except for mild secondary anemia the blood was normal. The Kahn test gave a negative reaction. The bilirubin content of the blood was 27 mg per hundred cubic centimeters (direct). The serum protein values were 66 per cent total protein, 24 per cent albumin and 42 per cent globulin, and the albumin-globulin ratio was 0.6. On November 12 the dextrose tolerance test showed the following values: fasting, 60, first hour, 114, second hour, 120, third hour, 75, and fourth hour, 33 mg, per hundred cubic centimeters.

On November 20 laparotomy was done. The pancreas was normal. The liver had an irregular nodular surface suggesting biliary cirrhosis. The common bile duct was involved in a mass of adhesions and was completely constricted. No type of reconstruction was possible, catheter drainage to the outside was instituted. A specimen of the liver was taken for biopsy, and the pathologist reported that it showed ascending cholangitis and beginning biliary cirrhoses.

CASE 6—T. R., a 51 year old housewife, was first seen at the University Hospital on Oct. 18, 1935, complaining of attacks of weakness, staggering and tinnitus. These attacks had come on periodically for five years at any time of the day. At the onset the local physician found sugar in the urine, and he restricted the intake of carbohydrate somewhat. The glycosuria rapidly disappeared, but the attacks (which were interpreted as hysterical) continued. A severe attack occurred eight months before entry. There had never been loss of consciousness, polyuria, polydipsia, polyphagia or spontaneous loss of weight. In the past year she had lost 35 pounds (16 Kg.) by caloric restriction.

Physical examination revealed a well nourished middle-aged woman who did not appear ill. The only abnormal physical finding was slight enlargement of the liver, the edge being firm and extending 2 cm below the right costal margin. There was tenderness to pressure in the right upper quadrant of the abdomen.

The urine and blood were normal, and the Kahn test gave a negative reaction. A cholecystogram showed normal visualization of the gallbladder, with a solitary semiopaque stone. There was abnormal rounding of the hepatic margin. A dextrose tolerance test showed the following values: fasting, 72, first hour, 224, second hour, 194, and third hour, 132 mg, per hundred cubic centimeters. All the specimens of urine except the one taken during fasting showed glycosuria.

The patient was discharged on November 14 with a maintenance dietary regimen for diabetes without insulin. She was considered to have extremely mild diabetes, since she tolerated a normal diet without glycosuria.

A year later, on Nov. 5, 1936, she returned, having had no glycosuria for six months with an unrestricted diet. She complained bitterly of attacks similar to those previously described but more severe. She now called these attacks "the jitters." During the attacks, which came on most frequently in the morning, she would experience "inward and outward trembling," profuse sweating and intense hunger. She found that food relieved the attacks quickly. There had been infrequent attacks of pain in the right upper quadrant of the abdomen but no jaundice.

The physical findings were the same as those of the previous year

A cholecystogram was made and disclosed faint visualization of the gallbladder, in which was seen a solitary semiopaque stone. It was noted that there had been progressive downward enlargement of the liver since the earlier examination. The tabulated results of the dextrose tolerance tests will be given later.

On the third, fourth and fifth days of the restricted carbohydrate diet, the blood sugar readings during fasting were 42, 57 and 47 mg per hundred cubic centimeters, respectively. The bromsulphalein excretion and the values for blood bilirubin, serum protein and red blood cells were normal. Two months later this same test gave blood sugar levels of 48 and 46 mg per hundred cubic centimeters.

On March 3, 1937, cholecystectomy was performed. The pancreas was grossly normal. The liver was grossly enlarged and exhibited a finely granular surface. The gallbladder was moderately thickened and contained a large stone. The gallbladder was removed, and a specimen of the liver was taken for biopsy.

The pathologist reported that examination of the gallbladder showed cholelithiasis, a solitary concretion being present. There was slight chronic cholecystitis, with slight cholestosis of the mucosal folds. The liver showed slight chronic interlobular hepatitis, with lymphocytic infiltration of the islands of Glisson. The inflammatory changes were relatively slight in the specimen studied. Staining showed irregular distribution of visible fat, the most marked storage being in the lobules which also showed the most marked inflammation. Staining for glycogen showed an abundant deposit, which was most marked around the central veins.

The results of the dextrose tolerance tests, in milligrams per hundred cubic centimeters, were as follows:

Date	Fasting	Hours				
		1	2	3	4	5
10/22/36	72	224	194	132		
1/14/37	77	205	130	56	49	
3/ 3/37	Operation					
9/14/37	96	222	100	55	61	71

On Sept 15, 1937, she was again given the restricted carbohydrate diet. After three days the blood sugar value during fasting fell to 38 mg per hundred cubic centimeters. Preoperative respiratory data indicated that the low blood sugar values were not accompanied by increased oxidation of dextrose (table).

Comment—In this case it appeared that, again, the glycogenolytic mechanism was the most seriously involved and that, although in the later stages the liver appeared to be capable of rapid glycogenesis, glycogenolysis remained impaired. The presence of large amounts of glycogen in the biopsy material from the liver also favored this interpretation. It was evident that glycogenesis was delayed earlier. This gave rise to the high plateau type of dextrose tolerance curve, which led to an erroneous diagnosis of diabetes mellitus. Spontaneous glycosuria had been found on several occasions. Oxidation of dextrose was found to be normal, however.

It is probable that those cases in which a diagnosis of diabetes mellitus has been made and the patient has been said to recover with the development of cirrhosis of the liver² were not cases of diabetes.

mellitus in the true sense. It is more likely that the original hyperglycemia and glycosuria were early manifestations of hepatic dysfunction and that the hyperglycemia was due not to decreased oxidative ability but to delayed glycogenesis.

COMMENT

An investigation was made to determine the nature of the disturbed carbohydrate metabolism associated with chronic ascending infectious hepatitis. Six patients were studied. All exhibited periods of spontaneous hypoglycemia. The glycemic response to ingested dextrose was grossly abnormal in several ways. A short period of fast or of carbohydrate restriction resulted invariably in severe hypoglycemia. Data obtained by indirect calorimetry indicated normal oxidation of dextrose under all of a variety of conditions. Besides the disturbance in carbohydrate metabolism, there were clinical and laboratory indications that other functions of the liver were also impaired. Microscopic examination of biopsy or autopsy material in these cases showed different stages of the same pathologic picture. Chronic cholecystitis and ascending infectious hepatitis leading to early biliary cirrhosis constituted the common pathologic change. Examination of the pancreas showed no abnormality either at operation or at autopsy.

We believe that this disturbance in carbohydrate metabolism, although common, is frequently unrecognized or wrongly interpreted. In the early stage the glycogenic function of the liver appears to be seriously impaired. This conclusion is reached as follows. In the well nourished normal organism, absorbed dextrose is disposed of by its simultaneous oxidation in the tissues and by the conversion and deposition of dextrose as glycogen in the liver and to a lesser degree in the muscles. Since our patients showed a hyperglycemic response after ingestion of dextrose and since they were shown to oxidize dextrose at the normal rate under the same conditions, the excess dextrose in the blood stream must be explained by impaired glycogenesis. We believe that this impairment in glycogenesis is one of rate rather than one of total disability since the blood sugar returns to the fasting level four to five hours after ingestion of dextrose and since removal of dextrose is not explained by increased oxidation. The slow rate of glycogenesis accounts for the prolonged hyperglycemia.

This delayed removal from the blood stream of absorbed carbohydrate results in postprandial hyperglycemia and glycosuria. Often this phenomenon has led to a diagnosis of diabetes mellitus (see cases 1 and 6). Our demonstration of normal oxidation of dextrose during this hyperglycemic period makes this diagnosis untenable. Recovery of the glycogenic function appears to parallel the disappearance of the active infection.

With the involvement of the glycogenolytic function of the liver periods of hypoglycemia become manifest. This situation may be easily mistaken for hyperinsulinism. Respiratory data obtained during the hypoglycemic phase of this disturbance indicate that the low blood sugar levels are not the result of overoxidation of dextrose, as is the case in true hyperinsulinism. That in proved hyperinsulinism, overoxidation of dextrose can be demonstrated by respiratory studies has been shown by Liu, Loucks, Chou and Chen¹⁷

It seems, then, that hyperglycemia and glycosuria simulating diabetes mellitus may be a manifestation of one phase of hepatic dysfunction and that periodic spontaneous hypoglycemia may be the manifestation of further hepatic injury in the same patient at different times in the course of hepatitis. This suggests that the hypothetical conception of "dysinsulinism," propounded by Harris¹⁸ to explain hyperglycemia in one period and spontaneous hypoglycemia in another in the same patient, is probably not the true underlying physiologic mechanism involved in many cases. Since oxidation of dextrose is normal in both the hyperglycemic and the hypoglycemic phases, it appears that hypoinsulinism alternating with hyperinsulinism is not the explanation.

Harris¹⁹ also stressed the fact that many patients with hyperinsulinism give a previous history of glycosuria. It should be recalled that close to 50 per cent of the patients operated on for hyperinsulinism have failed to disclose pancreatic abnormality²⁰. It is conceded that a tiny tumor of the islet tissue may be easily missed at operation. But in those cases in which partial or subtotal pancreatectomy has been done when a pancreatic tumor has not been found, the results have been notoriously unsuccessful in relieving the hypoglycemia. Hepatogenic hypoglycemia seems a more likely explanation. Even though the anatomic changes in the liver may be slight, the presence of chronic biliary infection may lead to marked functional disturbances in the metabolism of carbohydrate.

A short period of fast or sharp restriction of the intake of carbohydrate gave rise in our patients to extremely low blood sugar levels. It appears that this response to carbohydrate restriction is a sensitive

18 Harris, S. Nomenclature of Disorder of Insulin Secretion. Diabetes Mellitus, Hyperinsulinism and Dysinsulinism, Analytical Review of Data Relevant to Classification and Terminology of Secretory Disorder of the Islets of Langerhans of the Pancreas, *Ann Int Med* **7** 1084, 1934.

19 Harris, S. (a) Hyperinsulinism, a Definite Disease Entity. Etiology, Pathology, Symptoms, Diagnosis, Prognosis and Treatment of Spontaneous Insulogenic Hypoglycemia (Hyperinsulinism), *J A M A* **101** 1958 (Dec 16) 1933, (b) footnote 18.

20 Wilder, R. M., in discussion on Harris,^{19a} p 1964. Conn, J. W. The Advantage of a High Protein Diet in Spontaneous Hypoglycemia, *J Clin Investigation* **15** 673, 1936.

test of the ability of the liver to deal normally with carbohydrate. When all other indications of impaired hepatic function had returned to normal, this test still demonstrated an inability of the organism to maintain a normal blood sugar level during fasting.

In this type of hepatic dysfunction, all the classic symptoms of disease of the gallbladder or liver may be absent. This is well illustrated in several of our cases. Hence, patients who suffer from periodic spontaneous hypoglycemia or whose dextrose tolerance curves are suggestive of diabetes in association with a low blood sugar level during fasting should be investigated for the presence of infection of the biliary tract.

The cases of chronic hepatogenic hypoglycemia reported in the literature have been associated with incurable destructive or degenerative lesions of the liver. It is evident from our experience that the condition described may be greatly helped or even alleviated to the stage of clinical cure if the diagnosis of infectious hepatitis is made early and if appropriate surgical treatment is instituted.

CONCLUSIONS

A syndrome is described which is characterized by the presence of low blood sugar values during fasting, postprandial hyperglycemia and glycosuria and periodic attacks of spontaneous hypoglycemia.

Various stages of chronic ascending infectious hepatitis constitute the common pathologic lesion.

Such cases have been wrongly interpreted as examples of diabetes mellitus, hyperinsulinism or dysinsulinism.

Normal oxidation of dextrose was demonstrated under all the conditions studied.

Delayed hepatic glycogenesis and impaired glycogenolysis appear to account for the disturbance in carbohydrate metabolism.

The most sensitive test of the presence of this hepatic dysfunction is the occurrence of severe hypoglycemia after restriction of carbohydrate.

Clinical cure is possible after removal of the source of the hepatitis.

SPECIFICITY OF THE AGGLUTININ REACTION FOR SHIGELLA DYSENTERIAE

I AGGLUTINATION REACTION IN CHRONIC BACILLARY DYSENTERY,
A SEROLOGIC AND BACTERIOLOGIC STUDY OF
FORTY-SEVEN CASES

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The Widal test is conceded by certain investigators to be a highly important procedure in the diagnosis of infection due to *Shigella dysenteriae*¹. Agglutination of any of this group of organisms by the serum of a patient is said to warrant the diagnosis of past or present dysentery or of prophylactic vaccination, provided living antigens are not used in the performance of the test.

Interpretation of the test is subject to certain well recognized sources of error. Healthy persons frequently possess normal agglutinins for *S. dysenteriae*². The origin of these antibodies is uncertain. The responsible antigens are not known³. According to Arkwright⁴ the agglutinins usually are not demonstrable in dilutions above 1:100. Gardner,⁵ however, found that serum from normal persons may agglutinate strains of

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1 Davison, W. C. A Bacteriological and Clinical Consideration of Bacillary Dysentery in Adults and Children, *Medicine* **1**: 389-510 (Nov.) 1922. Gay, F. P., in Gay, F. P., and others. Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

2 Ritchie, T. R. On the Agglutination Reaction of the Bacilli of the Typhoid Dysentery Group with Normal Sera, *Lancet* **1**: 1257-1260 (June 24) 1916.

3 Tevel, Z. Dysenterieagglutinine, *Arch. f. Kinderh.* **108**: 1-13, 1936.

4 Arkwright, J. A. Agglutination, in A System of Bacteriology in Relation to Medicine, Privy Council, Medical Research Council, London, His Majesty's Stationery Office, 1931, vol. 6, chap. 12, pp. 381-423.

5 Gardner, A. D. The Dysentery Group of Bacilli as a Whole, in A System of Bacteriology in Relation to Medicine, Privy Council, Medical Research Council, London, His Majesty's Stationery Office, 1929, vol. 4, chap. 3, pp. 161-184.

Flexneri bacilli in dilutions up to 1:150. The titer of normal agglutinins is said to be raised by such varied stimuli as acute infectious diseases, transfusion and the exhibition of certain drugs.⁶ Furthermore, it appears that the average normal agglutinin titer for Flexneri bacilli varies in different localities according to the recent or the remote prevalence of bacterial dysentery of this type.⁷

Serologic diagnosis is further complicated by other factors. S-R dissociation is known to affect the specificity of the agglutination reaction. Immunization with an R antigen may produce a serum capable of agglutinating R or partially R dissociants of a number of unrelated species of bacteria.⁴ This mechanism has been advanced to explain the phenomenon of para-agglutination, which is said to occur frequently in the course of intestinal infections.⁸ This is characterized by the agglutination of organisms other than the known etiologic agent by the serum of persons convalescent from bacterial infection.

Although interpretation of the Widal reaction is thus subject to unavoidable error, certain of the hazards can be eliminated. The use of pure S strains minimizes group reaction. Utilization of standardized antigens prepared from these strains and treated with solution of formaldehyde further reduces the possibility of nonspecific agglutination.⁹ Selection of the titer level to be considered as establishing the diagnosis remains arbitrary, however. Ritchie,² working in England with living antigens, concluded that definite agglutination at 1:125 for Flexneri and at 1:64 for Shiga bacilli is significant. Dudgeon,¹⁰ using antigens treated with solution of formaldehyde, held that titers for Shiga bacilli of 1:40 and for Flexneri bacilli of 1:150 are diagnostic. He qualified

6 Rajchman, L., and Western, G. T. Reports upon the Investigations in the United Kingdom of Dysentery Cases Received from the Eastern Mediterranean. II. Report upon Eight Hundred and Seventy-Eight Cases of Bacillary Enteritis, Privy Council, Medical Research Committee, Special Report Series, no. 5, London, His Majesty's Stationery Office, 1917. Martyn, R. Wirkung der nicht spezifischen Faktoren auf den Agglutinationstiter bei Dysenterie, *Monatschr. f. Kinderh.* **66**: 16-21, 1936.

7 Havens, L. C. The Bacteriology of Typhoid, Salmonella, and Dysentery Infections and Carrier States, New York, Commonwealth Fund, Division of Publications, 1935.

8 Culbertson, J. T. Acquired Immunity. The Phenomenon of Agglutination, in Gay, F. P., and others. Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

9 Dudgeon, L. S. The Dysentery Group of Bacilli. B. Dysenteriae (Shiga) and Schmitz's Bacillus in A System of Bacteriology in Relation to Medicine, Privy Council, Medical Research Council, London, His Majesty's Stationery Office, 1929, vol. 4, chap. 3, pp. 184-220.

10 Dudgeon, L. S., and others. Studies of Bacillary Dysentery Occurring in the British Forces in Macedonia, Medical Research Council, Special Report Series, no. 40, London, His Majesty's Stationery Office, 1919.

this, however, by the statement that there is no evidence to indicate that any standard dilution can be accepted as establishing the presence of infection by the Flexner strains. Agglutination of the Sonne bacilli at 1:25 has been considered significant.¹⁰

The agglutinin titer seldom reaches high levels. Dudgeon¹⁰ found a titer of 1:480 in only 1 of 177 cases of acute Shiga dysentery. The majority were below 1:200. In only 104 of 211 cases of Flexner dysentery did the titer exceed 1:100. In only 6 cases were there agglutinins at dilutions above 1:500. The course of the agglutinin curves has been little studied except in acute infections. Patients with low titers rapidly lose their agglutinins during convalescence, provided there is no recurrence of symptoms. It is said that the agglutination reaction does not parallel the findings on culture in chronic dysentery. Glynn and Robinson¹¹ found that 60 per cent of the patients who were excreting Shiga bacilli gave a positive Widal reaction. On the other hand, the reaction was positive for only 20 per cent of those excreting Flexner bacilli.

TABLE 1—*Duration of Observation*

Months	Number of Cases
6-12	4
13-24	12
25-36	12
37-48	6
49	13
	<hr/> 47

Delayed convalescence or relapse causes the agglutinins to disappear more slowly. Under these conditions they may remain demonstrable for a considerable period.

We have observed fluctuation of the curves for individual agglutinin titers and discrepancies between these curves and the results of repeated culture for a group of patients under prolonged observation. These findings have led us to investigate the significance of the agglutination reaction in chronic bacillary dysentery.

MATERIAL

Forty-seven patients presenting cultural or serologic evidence of infection by *S. dysenteriae* were studied for periods varying from six to fifty-two months. Flexner or Sonne bacilli were recovered on one or more occasions from 13 of these patients. The remaining 34 had repeatedly sterile cultures throughout the period of observation. All 47 patients exhibited chronic ulcerative lesions of the colon of the type encountered in chronic bacillary dysentery.

¹¹ Glynn, E., and Robinson, A. L. A Report upon 2,360 Enteritis "Convalescents" Received at Liverpool from Various Expeditionary Forces, Medical Research Committee, Special Report Series, no. 7, London, His Majesty's Stationery Office, 1917.

Two additional groups of patients were utilized for control purposes. Isolated observations, with the same technic, were made on 103 patients chosen at random from those seen in hospital, dispensary and private practice. These patients presented a variety of medical and surgical conditions.

A group in excess of 50 patients with chronic ulcerative colitis were subjected to similar repeated serologic and cultural studies, the same technic being used. The intestinal pathologic condition did not differ from that observed in the group of patients constituting the basis of this report. The duration of observation was likewise comparable.

METHODS

Plates of MacConkey's medium and eosin and methylene blue agar were inoculated directly from the rectal mucosa at proctoscopic examination. After twenty-four hours of incubation, suspicious colonics were inoculated by stab into tubes of 0.5 per cent hormone agar. Motility was tested by clouding of the semisolid medium and by hanging drop preparations of eighteen hour broth cultures. Cultures of nonmotile organisms were then transplanted by stab to semisolid sugar mediums, to peptone broth and to bromeresol purple milk. Final readings for the sugar and for the milk mediums were made after twenty-one days of incubation at 37 C. Organisms conforming to the morphologic and cultural characteristics of *S. dysenteriae* were tested against monovalent rabbit serum obtained from animals immunized against *S. stock* strains of Shiga bacilli, serologic variants of the Flexner group and Sonne bacilli.

The following stock cultures were used throughout these studies:

Shiga	{		Obtained from the New York State Board of Health
Flexner	{	Karim-Kahn	Obtained through Prof. E. G. D. Murray, of McGill University
	{	PB 24	
	{	Y. Ledingham	American Type Culture Collection
	{	Logan	
	{	41	
	{	45	
Sonne	{	E. Ledingham	Obtained through Prof. E. G. D. Murray

The first four Flexner strains and the Sonne strain were subcultures of the type organisms used by Professor Murray in his studies of the serologic variants of *S. dysenteriae*.¹²

Bacilli presenting the morphologic and cultural characteristics of the *Salmonella* group were tested against monovalent paratyphosus A and B rabbit serums.

Blood for agglutination was taken from each patient at irregular intervals throughout the period of observation. After clotting had occurred, the supernatant serum was pipetted off and used for the Widal test.

Standardized antigens prepared from the stock strains of *S. dysenteriae* and treated with solution of formaldehyde were used exclusively for the agglutination tests. Agar cultures were transplanted twice daily for ten subcultures. Only smooth colonies were transferred. The tenth subculture was washed off with 0.85 per cent solution of sodium chloride containing solution of formaldehyde U. S. P. (diluted 1:100) and stored at ice box temperature. The suspensions

¹² Murray, E. G. D. An Attempt at Classification of *Bacillus Dysenteriae* Based upon an Examination of the Agglutinating Properties of Fifty-Three Strains, *J. Roy. Army M. Corps* 31:257 (Oct.-Nov.) 1918.

were all standardized to contain approximately 1,000,000,000 organisms per cubic centimeter except that of Shiga bacilli, which was standardized at 500,000,000 per cubic centimeter. The agglutinability of the antigens was then measured in homologous monovalent rabbit serum of known titer. A test was made for spontaneous agglutination, at the time each Widal test was made, by suspension in 0.85 per cent solution of sodium chloride. Standard agglutination tubes were used for all Widal tests. Equal parts of serum diluted with 0.85 per cent solution of sodium chloride and suspension of standardized antigen were added to each tube. The antigen serum mixtures were kept in the water bath at 55 C for four hours and then at ice box temperature over night before readings were made. In each instance the full titer of the patient's serum was measured as shown by definite though incomplete agglutination. The last tube showing definite clumping to the unaided eye was considered the end point. The upper limits of the agglutinin titers as determined by this method have been used throughout this study.

FINDINGS FOR CONTROL GROUPS

Serum from 6 of the 103 patients chosen at random agglutinated some strains of *S. dysenteriae* at a dilution of 1:160. One sample

TABLE 2—*Agglutinin Titers in Thirteen Cases in Which Cultures Were Positive*

Titer of Serum	Number of Cases		
	Shiga Agglutinins	Sonne Agglutinins	Flexner Agglutinins
1:40	4		
1:80	1		
1:160	1	2	3
1:320		2	8
1:640			1

agglutinated at 1:320. Four of these 7 patients gave a history of chronic or recurrent diarrhea. One was a healthy laboratory technician who was engaged in these studies, 1 had intestinal amebiasis and 1 had subacute bacterial endocarditis. Positive cultures were obtained for 2 others who gave a negative reaction to the Widal test.

The serum of control patients with chronic ulcerative colitis without exception gave repeatedly negative agglutination reactions and sterile culture.

FINDINGS FOR PATIENTS WITH POSITIVE CULTURES

In 13 of the 47 cases *S. dysenteriae* was obtained on culture. Flexner bacilli were recovered in 11 and Sonne bacilli in 2 cases. No case of Shiga infection was found. The maximum agglutinin titers observed for these patients were not high and were subject to marked variation. Only 1 patient showed agglutination at a dilution of 1:640. Agglutinins for the Flexner strains were most commonly encountered and tended to reach the highest levels. In only 1 instance were agglutinins for the Shiga bacillus observed at a dilution of 1:160.

The agglutinin curves in certain illustrative cases are discussed in detail and presented in graphic form.

The serum in 6 of the 13 cases in which culture was positive agglutinated the Shiga bacillus at dilutions of 1:40 or higher. In 5 of these 6 cases Flexner bacilli were recovered, and in 1 case a Sonne bacillus was obtained on culture. Partial agglutination at a dilution of 1:160 was the highest titer observed. This coincided with like titers for Flexner and for Sonne bacilli and with the isolation of a Flexner bacillus in case 12 (chart 1). This patient was studied for forty-two months. Flexner bacilli were recovered twelve times. After the initial agglutination reaction, the Shiga agglutinins disappeared and were not again demonstrable in five subsequent tests.

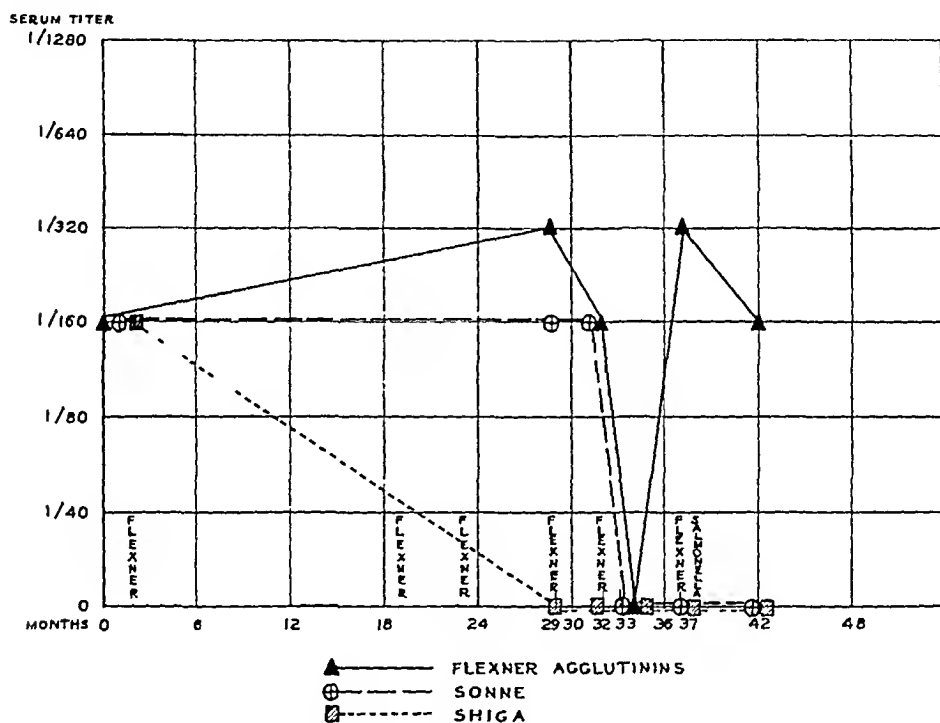


Chart 1 (case 12)—A total of twenty-two cultures were made. Flexner bacilli were present in twelve cultures.

Serum from 4 patients agglutinated the Sonne bacillus. In 2 cases the titer reached 1:320 and in 2 1:160. Flexner bacilli were recovered repeatedly from all 4 patients. Neither of the 2 patients from whom Sonne bacilli were isolated possessed demonstrable agglutinins for these organisms, despite repeated testing. However, only one positive culture was obtained for each.

CASE 12 (chart 1)—This patient carried a heavy Flexner infection throughout the forty-two months of observation. These organisms were recovered on twelve of twenty-two attempts. Serum from this patient agglutinated Sonne bacilli at a dilution of 1:160 at the initial determination, again at twenty-nine months and again at thirty-two months. Immediately thereafter the titer fell to zero and remained there.

CASE 8 (chart 2) —In this case no Sonne agglutinins were demonstrable at four determinations in the course of the first thirty-five months. Four months later, after Flexner bacilli had been recovered on three occasions, the titer for Sonne bacilli rose to 1:320, only to fall promptly to zero, rising again subsequently to 1:160 at two successive determinations.

Flexner agglutinins were invariably demonstrable at some time in all cases in which these organisms were recovered. The titer curve frequently showed marked and unaccountable fluctuation. Agglutination at a dilution of 1:640 was observed only once (case 2, chart 3). This patient was studied for fifty months. Flexner bacilli were recovered twice in nineteen cultures. At the outset no agglutinins for dysentery bacilli were demonstrable. Coinciding with the first positive culture, Flexner bacilli were agglutinated at a titer of 1:640. Four months later the titer fell to 1:40, followed after two months by a rise to 1:320. Another immediate fall, this time to zero, was followed by a third rise, reaching 1:320 at the last observation. It is of interest that this lightly infected patient gave the highest agglutinin titer of the group who showed positive cultures.

In case 8 (chart 2) the initial Flexner titer of 1:320 dropped to zero for two determinations prior to the recovery of Flexner bacilli, when agglutinins were again present at a dilution of 1:160. Four months later no Flexner agglutinins were demonstrable, although Sonne bacilli were agglutinated at a titer of 1:320. A second, sustained rise of the Flexner titer to 1:160 and 1:320 coincided with the isolation of an unidentified salmonella and *Bacillus alcaligenes*. Flexner bacilli were recovered three times in the course of thirty-four cultures in fifty-one months. In case 12 (chart 1) there was a drop in titer from 1:320 to zero, followed by an abrupt secondary rise to 1:320, within a period of eight months. This patient was heavily infected, yielding Flexner bacilli in twelve of twenty-two cultures throughout a period of forty-two months.

CASE 1 —This patient was studied for forty-three months. At the initial observation, Flexner agglutinins were present at a titer of 1:160. No Shiga or Sonne agglutinins were demonstrable. Thirty months later Flexner bacilli were isolated for the first time. The agglutination remained unchanged. In the course of the ensuing thirteen months Flexner bacilli were isolated on twelve different occasions. At thirty-two months the agglutinin titer for both Flexner and Sonne strains rose to 1:320 and for Shiga strains to 1:80. The Sonne titer remained unchanged at thirty-six, thirty-nine and forty-three months. Shiga agglutinins were absent at thirty-six months and did not reappear. The Flexner titer, however, fell to 1:160 at thirty-six and at thirty-nine months, rising again to 1:320 at the final determination. In this case, therefore, there was an abrupt and sustained rise of heterologous agglutinins immediately after the first positive culture was obtained. On two occasions subsequently the heterologous agglutinin titer exceeded the homologous titer.

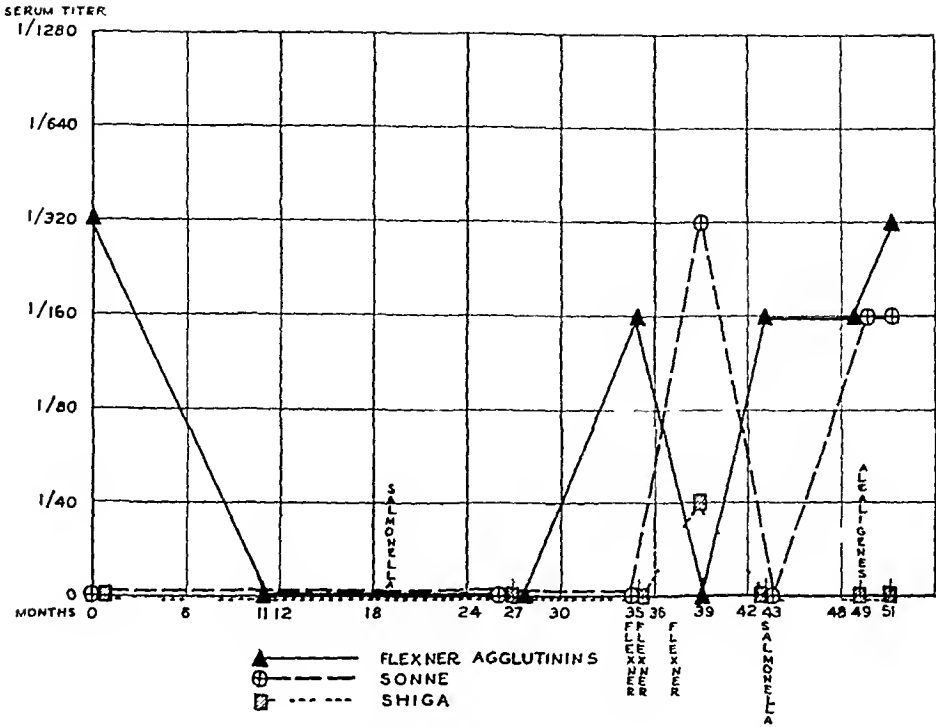


Chart 2 (case 8) —A total of thirty-four cultures were made Flexner bacilli were present in three

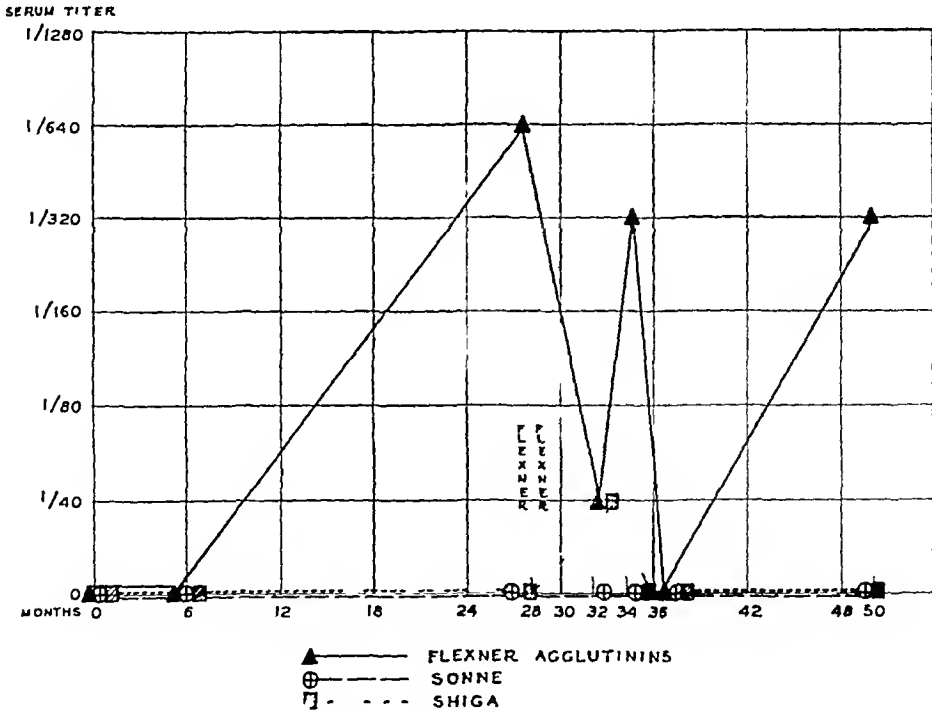


Chart 3 (case 2) —A total of nineteen cultures were made Flexner bacilli were present in two

CASE 3—This patient was studied inconstantly for forty-nine months. Flexner bacilli were recovered twice at the outset. Nine subsequent cultures were sterile. No agglutinins for any of the strains of *S. dysenteriae* were demonstrable when the two positive cultures were obtained. Three months later the Flexner titer rose to 1:160, only to fall again to zero at six months and at fourteen months. Flexner agglutinins were again demonstrable at a dilution of 1:160 at forty-nine months. No agglutinins for Shiga or Sonne bacilli were found at any time. In this case, therefore, there was a transitory low homologous agglutinin titer shortly after proof of the infection was obtained. Forty-six months later an equal secondary rise was observed, unaccompanied by cultural evidence of infection by *S. dysenteriae*.

FINDINGS FOR PATIENTS WITH STERILE CULTURES

In 34 cases in which cultures were consistently sterile, agglutinins for *S. dysenteriae* were found at titers usually considered as establishing the diagnosis. High titer reactions were more common for this group than for the group of patients for whom cultures were positive. Moreover, the highest titers observed for Shiga, Sonne and Flexner agglu-

TABLE 3—*Agglutinin Titer in Thirty-Four Cases in Which Cultures Were Sterile*

Titer of Serum	Number of Cases		
	Shiga Agglutinins	Sonne Agglutinins	Flexner Agglutinins
1:40	9		
1:80	5		
1:160	5	14	5
1:320	1	9	10
1:640		6	14
1:1280			1

tinins were found for the group of patients with sterile cultures. The agglutinin curves exhibited similar marked fluctuations.

In 20 of the 34 cases there was agglutination of Shiga bacilli at dilutions of 1:40 or higher. In 1 instance the titer reached 1:320, accompanying a titer of 1:160 for Flexner bacilli. The serum of 5 patients agglutinated Shiga bacilli at a dilution of 1:160.

CASE 18 (chart 4)—This patient was studied for twenty-six months. Seventeen sterile cultures were obtained. No Shiga agglutinins were demonstrable at the initial determination. In the following fourteen months the titer rose to 1:60 and fell again gradually to zero. A secondary rise to 1:80 at sixteen months was followed by disappearance of these antibodies. Throughout the period of observation, agglutinins for Flexner bacilli remained at a high titer, accompanied by a markedly fluctuating curve for Sonne bacilli.

CASE 31 (chart 5)—This patient was under observation for twenty-five months. Nineteen sterile cultures were obtained. An initial titer of 1:40 for Shiga bacilli fell to zero at six months, followed by a rise to 1:160 at seven months. Three months later Shiga agglutinins were absent, only to reappear at a titer of 1:80 at twelve months. After this observation they disappeared permanently. In this case likewise there was a high titer curve for both Flexner and Sonne bacilli.

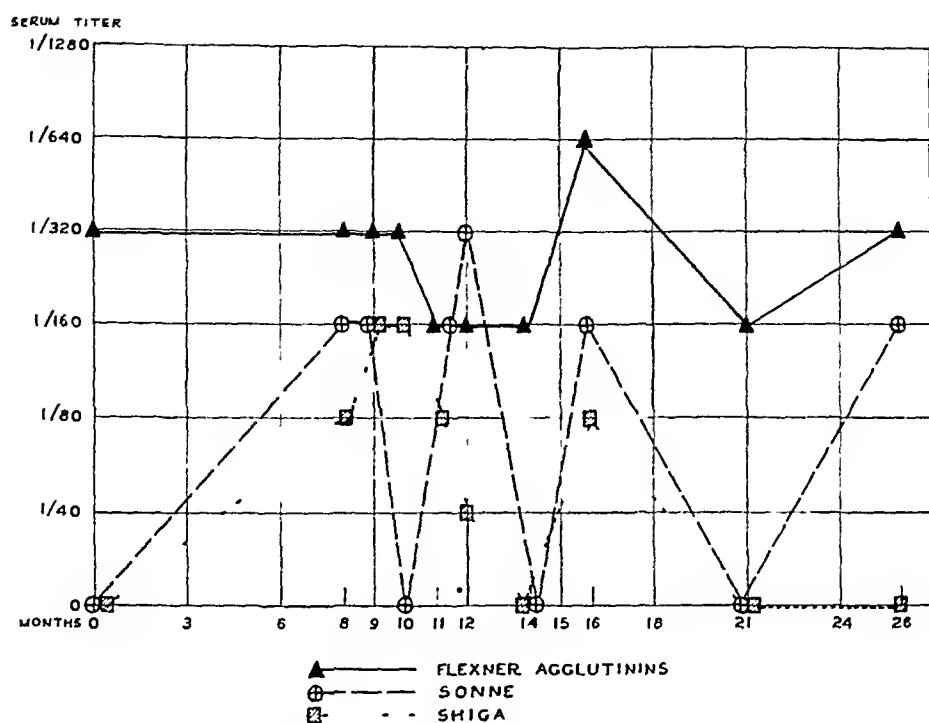


Chart 4 (case 18) —A total of seventeen cultures were made

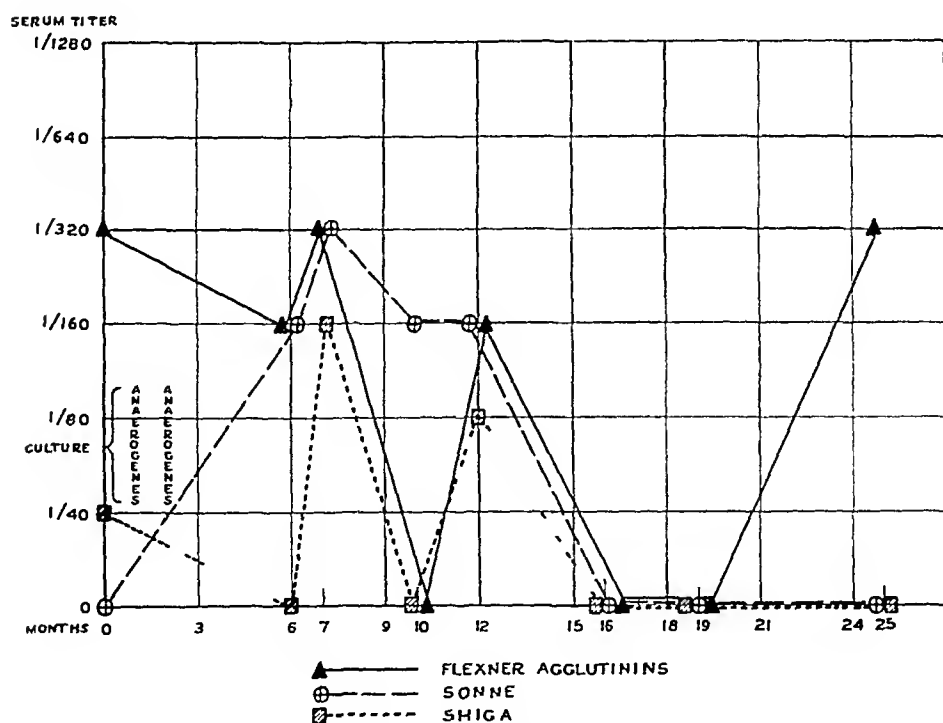


Chart 5 (case 31) —A total of nineteen cultures were made

The curves for the other patients exhibiting Shiga agglutinins presented essentially the same variations. None of the serums agglutinated the Shiga bacillus at a higher titer than it did the Flexner or the Sonne strains. A like titer for all three organisms was observed in 3 cases.

In 29 cases there was agglutination of Sonne bacilli at dilutions of 1/160 or above, in 6 of these cases reaching a titer of 1/640. The serum of 5 patients contained agglutinins for Sonne bacilli at a higher dilution than for either Flexner or Shiga bacilli. In general the Sonne agglutinin curves exhibited similar marked variations of titer.

CASE 41 (chart 6)—This patient was observed for twenty-six months, in the course of which thirty-nine sterile cultures were obtained. Throughout this

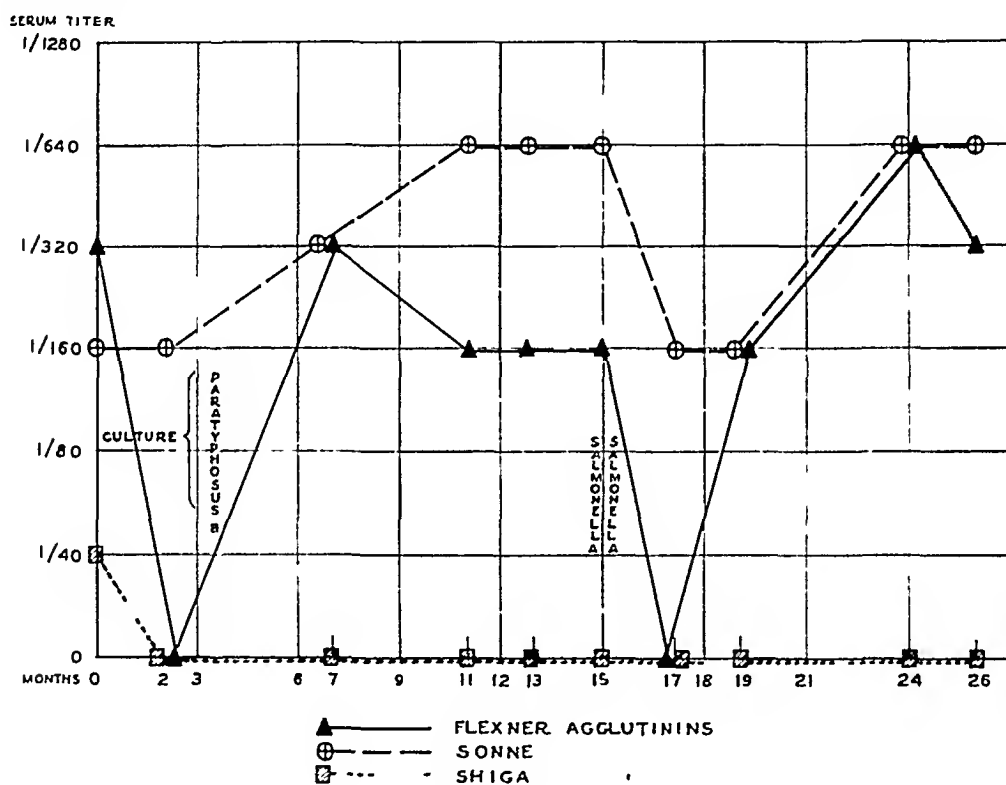


Chart 6 (case 41)—A total of thirty-nine cultures were made

period Sonne agglutinins were present at significant dilutions. The first two determinations revealed a titer of 1/160. This rose at seven months to 1/320 and at eleven months to 1/640, where it remained for two subsequent determinations. This was followed by a fall to 1/160 and subsequent rise to 1/640. In this case also there was an irregular Flexner agglutinin curve, which on one occasion reached a titer of 1/640.

CASE 31 (chart 5)—In this case there was a relatively smooth curve for Sonne agglutinins which did not parallel the curves for Shiga or Flexner agglutinins. The Sonne titer rose from zero to 1/160 at six months and to 1/320 at seven months. It then fell to 1/160 at ten and at twelve months and to zero at sixteen months.

Extreme fluctuations, however, were observed. In case 18 (chart 4) there was consistent agglutination of Flexner bacilli at dilutions varying

from 1 160 to 1 640 This was accompanied by a markedly fluctuating curve for both Sonne and Shiga bacilli The curve for the Sonne agglutinins did not parallel the curves for the other two organisms Starting at zero, Sonne agglutinins rose to 1 160 at eight and at nine months and returned to zero at ten months At eleven months they again rose to 1 160 and at twelve months to 1 320, followed by a drop to zero at fourteen months At sixteen months the Sonne bacilli were again agglutinated at a titer of 1 160, but a negative reaction was obtained at twenty-one months, followed by another rise at twenty-six months Seventeen cultures were sterile for *S. dysenteriae*

In 30 of the 34 cases there was agglutination of Flexner bacilli at dilutions of 1 160 or higher High titers were more common for Flexner strains than for either Shiga or Sonne strains In 1 instance the Flexner titer reached 1 1,280 The curves of the Flexner agglutinins showed irregularities similar to those of the curves for the other organisms and did not parallel the curves of the Shiga and the Sonne agglutinins

CASE 18 (chart 4) —This patient presented a Flexner titer of 1 320 on four occasions in the first ten months At eleven, twelve and fourteen months the curve fell to 1 160 This was followed by a rise to 1 640 at sixteen months, another fall to 1 160 at twenty-one months and a further rise to 1 320 at twenty-six months The Shiga and the Sonne agglutinins varied markedly during the period of observation

CASE 31 (chart 5) —In this case there was agglutination of Flexner bacilli at a dilution of 1 320 at the initial determination The titer fell to 1 160 at six months and rose again to 1 320 at seven months Three months later Flexner agglutinins were not demonstrable At twelve months agglutinins were present at a dilution of 1 160 The curve then again fell to zero at sixteen and at nineteen months, followed by a rise to 1 320 at the last determination

CASE 41 (chart 6) —This patient likewise revealed a fluctuating titer for Flexner bacilli in the course of ten determinations over a period of twenty-six months Starting at 1 320, the curve fell to zero at two months After the isolation of a salmonella agglutinating at low titer in paratyphosus B serum, Flexner agglutinins again rose to 1 320 The titer remained at 1 160 at eleven, thirteen and fifteen months, again falling to zero at seventeen months The curve then rose again to 1 160 at nineteen months and to 1 640 at twenty-four months, thereafter falling to 1 320 at the final determination This patient presented a consistently higher titer for Sonne agglutinins

CASE 45 —This patient presented the highest titer which we have seen The titer for agglutinins for Flexner bacilli reached 1 1,280, and that for Sonne bacilli reached 1 640 Cultures of the stool in another institution just prior to this finding were sterile, and five cultures of rectal mucosa made during the ensuing twelve months also failed to reveal *S. dysenteriae* Death occurred at the end of this period Postmortem cultures of samples from the colon and the ileum were sterile

CASE 15—This patient was under observation for seventeen months in the course of which fifteen sterile cultures were obtained. At the initial determination Sonne agglutinins were present at a dilution of 1:640. Coincidentally a salmonella agglutinating at a titer of 1:320 in paratyphosus B serum was isolated. At three and at eight months no dysentery agglutinins were demonstrable. At sixteen months Sonne and Flexner agglutinins were present at a dilution of 1:160. One month later the Flexner titer remained unchanged, and Sonne agglutinins were absent.

CASE 17—This patient was under observation for twenty-four months. Sixteen sterile cultures were obtained. No dysentery agglutinins were demonstrable at the initial determination. Twelve months later Shiga bacilli were agglutinated at a titer of 1:320 and Flexner bacilli at 1:160. At twenty-four months both Shiga and Flexner agglutinins were absent. However, Sonne agglutinins, previously not demonstrable, were obtained at a titer of 1:320.

CASE 21—This patient was under observation for sixteen months. Eleven sterile cultures were obtained. The initial Flexner titer was 1:160, the titer rose to 1:320 at three and at five months and to 1:640 at seven months, where it remained constant for three subsequent determinations at eleven, twelve and sixteen months. Sonne agglutinins were present at a titer of 1:320 at the first examination, the titer rose to 1:640 at three months, fell to 1:320 at five months and rose again to 1:640 at seven months. At eleven months the titer dropped again to 1:320 and at twelve months to 1:160. At the final determination it was again at 1:640. Agglutinins for Shiga bacilli were present at a titer of 1:80 at the first examination, the titer rising to 1:160 at three months. There was no agglutination at five, seven and eleven months. At twelve months the titer had risen to 1:80, and agglutination was again absent at the last determination.

CASE 27—This patient was under observation for twenty-two months. Twenty-five sterile cultures were obtained. No dysentery agglutinins were demonstrable at the initial determination. At five months a Flexner titer of 1:320 was found, falling to 1:160 at nine months and rising to 1:640 at thirteen months. This was followed by a fall to 1:160 at sixteen months and a further rise to 1:320 at eighteen months and to 1:640 at twenty-two months. Sonne agglutinins were present at a titer of 1:320 at five months, the titer falling to 1:160 at nine and at thirteen months. There was no agglutination at sixteen and at eighteen months, but the titer was again at 1:160 at the final observation. Shiga agglutinins were absent throughout except at five months, when a titer of 1:80 was found.

CASE 35—This patient was under observation for fifty-two months. Thirty-one sterile cultures were obtained. Three determinations in the first thirteen months failed to demonstrate agglutinins for dysentery bacilli. At twenty-five and at thirty-five months Flexner agglutinins reached a titer of 1:160. This rose to 1:320 at forty-two months. A fall to 1:160 at forty-five months was followed by a rise to 1:640 at fifty-two months. Sonne agglutinins were absent throughout except for the final determination, when a titer of 1:160 was found. Shiga bacilli were not agglutinated at any time.

COMMENT

The data obtained in these studies suggest the need for caution in the interpretation of the agglutination reaction. High serum titers do

not regularly accompany chronic infections due to *S dysenteriae*. In the course of a heavy long-continued Flexner infection, the patient's serum may contain agglutinins at equal titer for the Shiga, the Sonne and the Flexner bacillus. Sonne organisms may be agglutinated to a higher titer than Flexner organisms in the course of proved infection. Agglutinins for the Flexner strains may maintain a relatively constant level, or they may fluctuate markedly, often disappearing temporarily in the course of proved homologous infection.

It has not been possible to correlate the variations in agglutinin titer with the associated bacterial flora, with the clinical condition of the patient or with the condition of the lower portion of the colon as seen at proctoscopy. Moreover the height of the agglutinin titer does not appear to be a measure of the chronicity or of the intensity of the infection. Only two positive cultures for *S dysenteriae* were obtained for the patient with the highest agglutinin titer. Of the 9 patients presenting agglutinins at dilutions of 1:320 or higher, only 3 yielded more than 6 positive cultures.

The predominance of higher titers for all three of the strains of *S dysenteriae* in the cases in which culture was sterile is striking. Not even the most heavily infected patients possessed agglutinins at levels frequently found for patients who repeatedly yielded sterile cultures. As was the case in the group of patients with proved infection, the agglutinin curves were subject to marked and irregular fluctuation from zero to relatively high levels in the course of a few months, or a consistently rising titer was encountered. Frequently there was a complete lack of parallelism between the individual agglutinin curves for Shiga, Sonne and Flexner bacilli for the same patient. Again, it has not been possible to correlate these findings with demonstrable changes in the clinical condition, the associated bacterial flora or the appearance of the mucosa of the lower portion of the colon.

For both the patients who showed positive cultures and those who showed sterile cultures, the Flexner agglutinins were demonstrable at higher dilutions than the Sonne or the Shiga agglutinins. The Sonne agglutinins occupied an intermediate position. Agglutinins for Shiga bacilli were rarely encountered at dilutions of 1:160 or higher.

Certain of these findings raise a question as to the specificity of the Widal reaction in chronic dysentery. It is more difficult to concede specificity in the face of lower average agglutinin titers when culture is positive than when it is sterile. It is difficult to explain the marked variations in the curves observed for both groups of patients. The association of Sonne agglutinins at equal or at higher titers than those for Flexner bacilli in the course of a heavy Flexner infection is contrary to expectation.

It is unlikely that normal agglutinins for *S. dysenteriae* are responsible for these facts. The findings for the two control groups strongly suggest that normal agglutinins are not common in persons living in the city of New York and that they do not ordinarily reach a high titer. It is recognized, however, that isolated observations cannot be completely satisfactory, especially in view of the variations in titer observed in the cases under discussion.

The anamnestic reaction may be advanced to explain the persistence of agglutinins in the cases in which cultures were sterile. Yet it is

TABLE 4—Associated Bacteria in Thirteen Cases in Which Cultures for *S. Dysenteriae* Were Positive

Bacteria Recovered	Number of Cases
<i>S. dysenteriae</i> Flexner	11
<i>S. dysenteriae</i> Sonne	2
<i>Salmonella</i> , unidentified	3
<i>Paratyphosus</i> B	1
<i>Pyocyaneus</i>	2
<i>B. coli</i> anaerogenes	1
<i>B. alealescens</i>	1
<i>B. faecalis</i> alealigenes	2
Beta hemolytic streptococci	4
Nonhemolytic streptococci	2

TABLE 5—Associated Bacteria in Thirty-Four Cases in Which Cultures for *S. Dysenteriae* Were Sterile

Bacteria Recovered	Number of Cases
<i>Salmonella</i> , unidentified	16
<i>Paratyphosus</i> B	5
<i>Paratyphosus</i> A	1
<i>B. morgani</i> 1	4
<i>B. coli</i> anaerogenes	4
<i>B. alealigenes</i>	2
<i>B. proteus</i>	5
<i>B. fluorescens</i>	1
<i>B. pyocyaneus</i>	1
Beta hemolytic streptococci	7
Nonhemolytic streptococci	7

unlikely that such a mechanism should frequently give rise to agglutinins for *S. dysenteriae* at higher titers than those observed in cases of proved homologous infection.

It is recognized that sterile cultures do not constitute proof that an organism is absent. The Flexner bacilli especially are notoriously difficult to recover. The mediums used in these studies, the number of cultures taken, the technic of culture and the duration of the period of observation indicate that if *S. dysenteriae* was present, the infection must have been light.

The possibility that the agglutinins for *S. dysenteriae* may be produced as a nonspecific response to infection of the colon by other types of bacteria remains to be considered. Heterologous R agglutination was

guarded against throughout these studies by the use of antigens, treated with solution of formaldehyde, prepared from S strains of known agglutinability in homologous and heterologous antidyentery rabbit serums

The possibility of para-agglutination⁸ cannot be definitely eliminated. The cultural studies of these patients included repeated search for S dysenteriae and for other potential pathogens which might play a role in the production of the intestinal pathologic condition. Exclusive of *Escherichia coli*, various members of the salmonella group were recovered more frequently than any other species of bacteria (tables 4 and 5). These organisms were isolated in 28 of the 47 cases. Although this constitutes a high rate of incidence, it cannot be interpreted to explain the production of nonspecific agglutinins. Furthermore, the agglutination reactions of these strains of *Salmonella* in serum of patients and in the monovalent dysentery rabbit serum failed to indicate any cross immunologic relationship between these organisms and S dysenteriae. It is impossible to confirm or to refute the potential role of para-agglutination in these cases at present.

The relation between the production of S dysenteriae agglutinins and heterologous infection will be detailed in a subsequent communication.

SUMMARY

Prolonged serologic and cultural studies indicate the necessity for cautious interpretation of the agglutination reaction in cases of chronic inflammatory disease of the colon. We have repeatedly found agglutinins for S dysenteriae present at titers commonly considered to establish the diagnosis unaccompanied by cultural evidence of homologous infection. Conversely, no agglutination reactions have been observed in cases of proved infection. Marked and unaccountable variations of agglutinin titer are the rule in the course of repeated determinations. It is a striking fact that the majority of the serums which gave a high titer were obtained from patients who consistently showed sterile culture for S dysenteriae. These observations suggest that agglutinins for S dysenteriae may develop in response to nonspecific heterologous stimuli.

RELATION OF AGE TO RENAL PRESSOR SUBSTANCE

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Elevation of the blood pressure is rare in children, occurs occasionally in young adults and appears frequently in elderly persons. Any satisfactory hypothesis of the mechanism of hypertension must necessarily explain the striking variations in the frequency of this disorder at different ages. In the course of an investigation of the possible relation of the renal pressor substance (the renin of Tigerstedt and Bergman¹) to certain types of experimental hypertension, we have compared the sensitivity of rats of different ages to this agent. Studies have also been made of the amount of pressor substance in the kidneys of such rats.

METHOD

Fresh kidneys of hogs were obtained from the slaughter house. The renal cortex was separated from the medulla, passed through a meat grinder and then ground to a fine paste with carborundum. Ninety-five per cent alcohol was then added, in a ratio of 9 cc to 1 Gm of cortical tissue. The mixture was allowed to stand in the ice box for twenty-four hours or longer and then centrifuged while still cold. After the supernatant alcohol had been poured off, the residue was treated with ether and then spread out on flat plates and dried under a fan. The dry powder was ground in a mortar with 0.5 per cent sodium bicarbonate at a temperature of 40 to 45 C. After centrifugation the supernatant fluid was saved, and the residue was twice reextracted, the total amount of bicarbonate solution added being equal to 2 cc per gram of original renal cortex. The supernatant fluids obtained by centrifugation after the extractions were mixed and kept in the ice box until the time of injection.

Rats of known age were obtained either from the Wistar Institute or locally.² The sensitivity of these rats to renal extract was determined as follows. Pentobarbital sodium (3 or 4 mg per hundred grams of body weight) was administered intraperitoneally. The abdomen was then opened, and a needle (22 to 16 gage) was tied into the lower abdominal aorta. By means of a three way stop-cock this needle could be connected either to a small bore mercury manometer for direct reading of the aortic blood pressure or to a syringe for the injection

From the Department of Medicine, Vanderbilt University.

This investigation was aided by a grant from the Josiah Macy Jr Foundation.

¹ Tigerstedt, R, and Bergman, P. G. Niere und Kreislauf, Skandinav Arch f Physiol 8 223, 1898.

² Dr Karl Mason, of the department of anatomy supplied some of the rats used in this work.

of solution into the aorta. A small amount of solution of heparin was injected in order to prevent clotting. The amount of renal extract given was calculated according to the following formula

$$\frac{(\text{Body weight in grams})^{2/3} \times 2}{100} = \text{cubic centimeters to be injected}^3$$

It was thought that the body surface, which is proportional to the two-thirds power of the weight, would be a more reliable index of dosage than the body weight. It should be noted that the smaller rats received considerably larger doses in proportion to the body weight than did the larger rats. After the injections the blood pressure was read at intervals of fifteen seconds for a period of thirty minutes.

The results obtained for a given rat were discarded when (a) the initial mean arterial blood pressure was below 90 mm of mercury, (b) the animal died within the thirty minute period after receiving the injection or (c) a marked decline in blood pressure (below the initial level) occurred before the end of the thirty minute period. For purposes of comparison the values obtained for 3 to 6 animals in each age group were averaged.

Prior to the insertion of the needle into the aorta, the kidneys of the rat were removed, weighed, ground and treated with 9 volumes of 95 per cent alcohol. The kidneys of the rats of a given age group were then mixed, and an extract was prepared by the same technic as that used for hog kidneys. This extract was then tested on other rats, according to the technic just described, female rats approximately 4 months of age being used.

RESULTS

In the first experiment three groups of female rats were studied, their ages being approximately 10 weeks, 1 year and 2 years, respectively. The youngest were decidedly less responsive than the two groups of older rats, the 1 year old animals being slightly more sensitive than the 2 year olds.

In the second experiment three groups of male rats were used. Again the youngest rats displayed the smallest rise in blood pressure, but in this series the oldest rats (2 years) were somewhat more sensitive than the animals of intermediate (1 year) age.

A third experiment was then carried out on rats of both sexes that were 6 weeks, 6 months, 1 year and 2½ years old, respectively. The results of this experiment, which are shown in chart 1, indicated again that the youngest rats were the least sensitive. The senile (2½ years) rats gave the greatest rises in blood pressure. Consistent differences between the rises in blood pressure obtained in the two intermediate age groups (6 months and 1 year) were not observed, the values for both of these groups falling between those for the immature (6 weeks) and those for the senile (2½ years) animals.

The data were then analyzed from the standpoint of the sex of the rats, but no consistent differences between the pressor responses of

³ Thus a rat weighing 100 Gm would receive 0.43 cc, one weighing 200 Gm, 0.68 cc, etc.

males and those of females of a given age were noted. Accordingly, all the figures for animals of the same age groups, regardless of sex, were combined, and the averages were computed. The curves for the animals of the intermediate groups (6 months, 1 year and 2 years) crossed each other several times (chart 2) and displayed no consistent differences. However, the youngest rats (6 to 10 weeks) showed the least response and the oldest rats ($2\frac{1}{2}$ years) the greatest response (chart 2). The differences observed could not be ascribed to variations in the initial blood pressure levels, for these showed no consistent relation to the age of the animals.

In order to determine whether the differences in sensitivity were due to a general increase in sensitivity to pressor agents with increasing age, the animals used in the third experiment were given injections of 1:2,000,000 solution of epinephrine hydrochloride, the doses being calculated in the same way as when renal extract was used. Consistent differences in the response to epinephrine of the animals of different ages were not observed, the general tendency being for the older animals to be slightly less sensitive than the younger ones (chart 1).

The data were next analyzed from the standpoint of the body weight. No consistent relation between this factor and the sensitivity of the animal was observed. Thus, for the experiment recorded in chart 1, the 6 month old males happened to be larger than any of the other animals. Their average body weight was 415 Gm, while the averages for the $2\frac{1}{2}$ year old animals were 366 Gm for males and 275 Gm for females. However, these senile animals displayed a considerably greater rise in blood pressure than did the larger, 6 month old rats. Furthermore, if the increased response of the senile rats and the diminished sensitivity of the immature rats were due mainly to difference in size, one would expect males to show greater responses than females of the same age. Such was not the case. The size of a rat is evidently less important than its age in determining its sensitivity to renal pressor substance.

The pressor effects of renal extracts made from rats of different ages were compared by injecting the extracts into other rats. Two methods of comparison were used.

1. Two rats were given injections of the extracts of the kidneys of rats of each age group, the blood pressure being followed for thirty minutes, as in previous experiments. The greatest rise in blood pressure was obtained from the extract of the kidneys of the youngest rats, the least rise from that of the oldest rats and the intermediate response from that of rats of intermediate age (chart 3). No significant difference was found between the pressor effect of extract of kidneys of male and that of female rats of the same age.

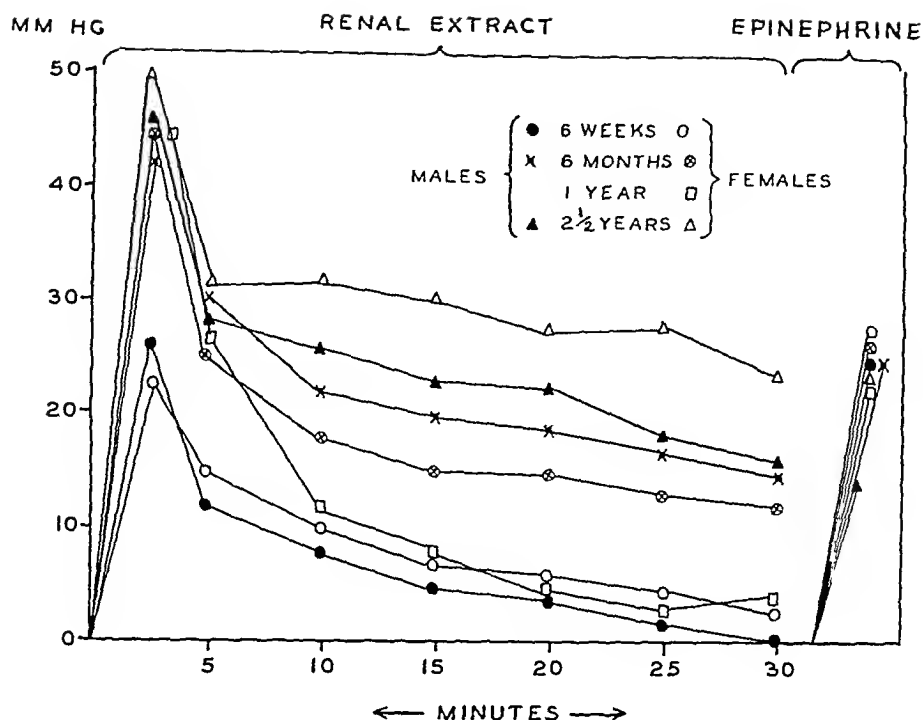


Chart 1—An example of a day's experiment Each curve represents the average blood pressure response of 2 to 5 rats that were given renal extract, as explained in the text It will be seen that the young rats are the least sensitive and the senile ones the most sensitive and that the curves for the groups of rats of intermediate ages fall between the curves for these two groups There is overlapping of the curves for the intermediate groups There is no consistent difference with regard to sex The column of figures to the left shows the rise in mean arterial blood pressure after the injection of renal extract

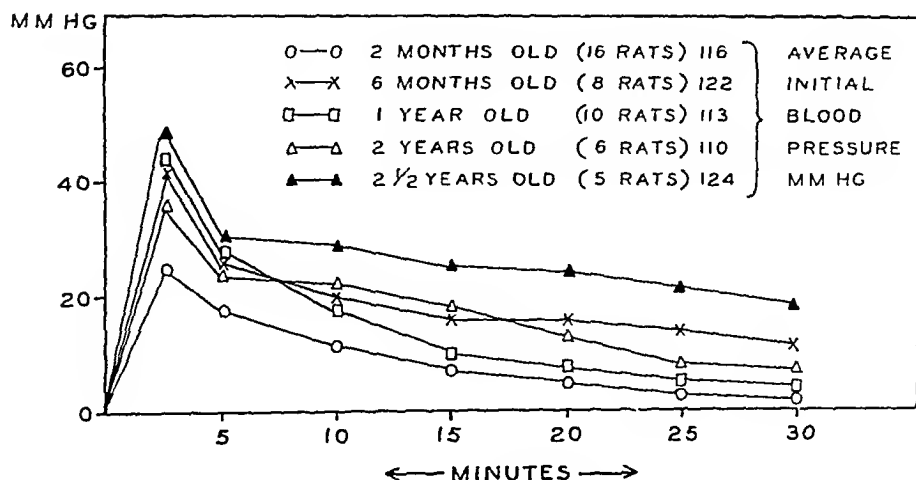


Chart 2—A composite chart of the results of all three experiments As shown in chart 1, the old rats are the most sensitive and the young rats the least sensitive, and there is again some overlapping of the curves for the intermediate groups, which fall between those for the oldest and the youngest rats The column of figures to the left shows the rise in mean arterial blood pressure after the injection of renal extract

2 Comparisons were made by giving a group of rats alternate injections of the extract of kidneys of younger and that of older rats. Because of the marked decrease in response to successive doses, the effect of the injection of a given extract was compared with the average effect of the preceding and of the succeeding injection of the extract to be compared with it. Twenty such comparisons were made. In 15 instances the extract of the kidneys from the younger rats gave a greater pressor effect than did that from the older rats. In no instance was a greater effect obtained from "old" kidney than from "young" kidney. Five comparisons yielded inconclusive results, i. e., the pressor responses did not differ more than 5 mm. Four comparisons were

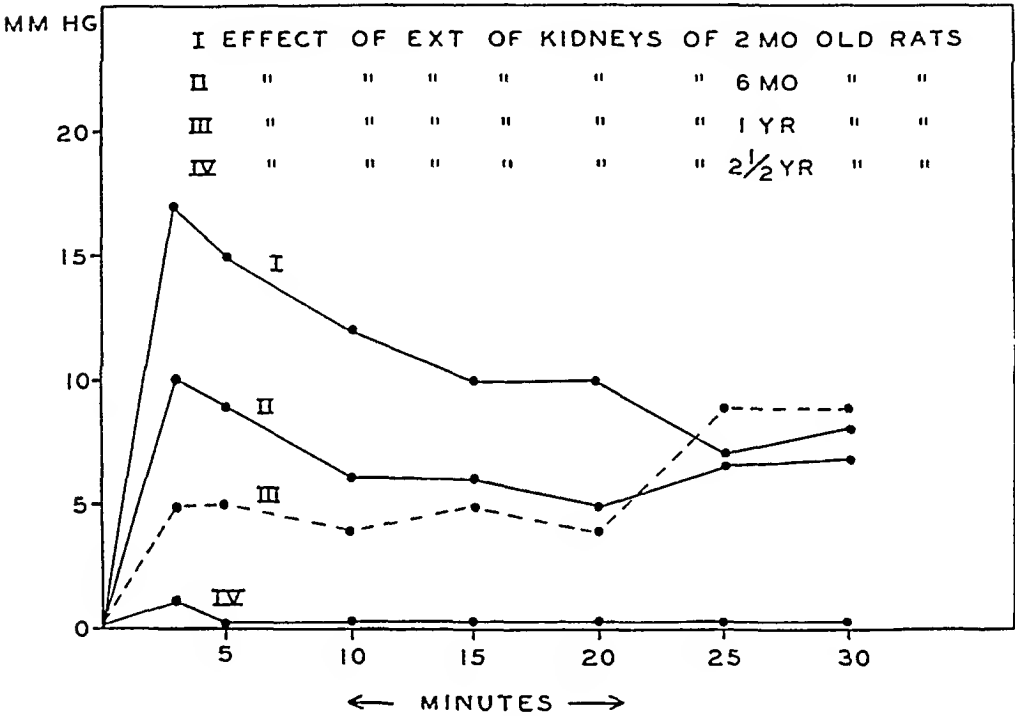


Chart 3—This chart represents the average rises in blood pressure produced by renal extracts of rats of various ages in 4 month old female rats. It shows the oldest rats to have the least pressor substance and the youngest rats the most, with the curves for the intermediate rats falling between in their proper order. The column of figures to the left shows the rise in mean arterial blood pressure after the injection of renal extract.

made of renal extract obtained from the kidneys of male and that of female rats of the same age. In each instance no significant difference was found.

These experiments indicate clearly that in rats the amount of renin in the kidneys diminishes with advancing age.⁴

⁴ Since this report was written we have found that the kidneys of calves contain more renin than those of adult cattle.

The data which have been presented show clearly that with advancing age the amount of pressor substance (per unit of renal weight) in the kidneys diminishes progressively. The data also show that senile rats are more responsive and immature rats less responsive to a given dose of renin than are rats of intermediate ages⁵. There seems to be relatively little difference in the sensitivity of groups of mature rats of different ages short of senility, but senile rats are definitely more sensitive than mature adult animals.

Whether renal pressor substance (renin) is related in any way to the tendency of elderly persons to show hypertension is not known. If such a relation does exist, it appears to be concerned with a disturbance in the capacity of the older organism to destroy, neutralize, excrete or otherwise overcome the effects of renin rather than with increased formation of this substance by the kidney.

SUMMARY

Extracts containing renal pressor substance (renin) were administered to rats of various ages in doses proportional to the body surface. The youngest rats (6 to 10 weeks) showed the least rise in blood pressure, the oldest (2½ years) displayed the greatest pressor effect and intermediate responses were displayed by rats of intermediate age (6 months to 2 years). On the other hand, the youngest rats had the most pressor substance in their own kidneys, and the oldest rats had the least.

The greater sensitivity of the oldest animals to renal pressor substance did not appear to be dependent on a general increase in reactivity to all pressor agents, for the administration of epinephrine produced as great a rise in blood pressure in the young as it did in the older animals.

The experiments suggest a possible relation between the increased sensitivity of senile rats to renal pressor substance and the tendency of elderly persons to show hypertension. However, it is concluded that no convincing evidence of such a relation exists at present.

⁵ This statement applies when doses are given according to body surface. If doses are given according to body weight, the difference between the sensitivity of young and that of old rats is still greater.

RELATION OF RENAL PRESSOR SUBSTANCE TO HYPERTENSION OF HYDRO- NEPHROTIC RATS

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In the course of investigations concerning the renal pressor substance (Tigstedt's renin) we have encountered a number of rats with spontaneous hydronephrosis. Such animals are usually found to have an elevation of blood pressure. The following investigations were undertaken to obtain information concerning the mechanism of the rise in blood pressure displayed by these animals.

METHODS

After anesthesia had been induced by the intraperitoneal injection of pentobarbital sodium, the blood pressure was measured by cannulation of the abdominal aorta with a needle attached to a small bore manometer, heparin being used to prevent clotting. The renal pressor substance was prepared from pig kidneys by precipitation with alcohol and extraction with dilute solution of sodium bicarbonate according to the technic described by Grossman¹.

Observations of two different types were made. In one series of experiments the sensitivity of hydronephrotic rats to renal pressor substance was compared with that of normal animals of the same size and of approximately the same age. For this purpose all the animals received doses calculated according to the following formula:

$$\frac{\text{Body weight in grams}^{2/3} \times 2}{100} = \text{cubic centimeters to be injected}$$

After this the blood pressure was read from the manometer at frequent intervals for thirty minutes. In a second series of experiments the pressor effects of hydronephrotic and of normal kidneys of rats were compared by making saline extracts and injecting these into normal rats. For this purpose the kidneys were ground with carborundum, a measured amount of 0.9 per cent solution of sodium

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* Fellow of the Commission for Relief in Belgium of the Educational Foundation, Inc

1 Grossman E B. A Note on the Preparation of Extracts of the Renal Pressor Substance, Proc Soc Exper Biol & Med, to be published

chloride was added and the mixture was ground further and then centrifuged. The supernatant fluid was injected in doses calculated according to the aforementioned formula.²

In order to compare the effects of spontaneous and those of induced hydronephrosis, experiments were also done on rats in which one ureter had been ligated two to seven days previously. The sensitivity of these animals to standard renal extract was compared with that of normal rats, and the pressor properties of saline extract of the normal and those of the saline extract of the obstructed kidney from the same rat were compared according to the indicated technique.

RESULTS

The Blood Pressure of Hydronephrotic Rats—A comparison between 4 rats with well marked bilateral hydronephrosis, 5 rats with unilateral hydronephrosis and 1,207 rats without hydronephrosis is shown in chart 1. The values for the blood pressure of normal rats were obtained from animals used in acute experiments in this laboratory in which they were kept under environmental conditions similar to those of the hydronephrotic rats. The chart shows clearly that each of the 4 rats with bilateral hydronephrosis had well marked hypertension. Of the 5 rats with unilateral hydronephrosis, 2 had a blood pressure well within the normal range (115 and 125 mm of mercury, respectively), and 3 had a blood pressure at the extreme upper limit of the normal range (155, 155 and 165 mm of mercury, respectively).

Another difference sometimes noted between the normal and the hydronephrotic rats was the tendency for the latter to exhibit a steady spontaneous decline in blood pressure. Under the conditions of our experiments normal rats usually displayed relatively little decline in blood pressure during a period of an hour or more. Hydronephrotic rats, on the other hand, tended to have a maximal value for blood pressure immediately after insertion of the aortic cannula, after which a slow decline sometimes ensued. This difference is illustrated in chart 2.

The Sensitivity of Hydronephrotic Rats to Renal Pressor Substance—Since it has been shown in a previous publication from this laboratory (Grossman and Williams³) that the age of the animal is an important

2 In order to allow for a greater amount of fibrous tissue in hydronephrotic than in normal kidneys, an attempt was made to estimate the amount of functioning renal tissue and to add to the abnormal kidneys sufficient saline solution so that the final ratio would be approximately 4 cc of salt solution per gram of functioning renal tissue, this ratio being used also in the case of the normal kidneys. Such a procedure resulted in extracts which could not be regarded as strictly comparable in a quantitative sense. This objection, however, did not apply to the experiments done later on rats with one ureter ligated, for here the abnormal kidney weighed approximately the same as the opposite normal organ of the same animal and contained no excess of fibrous tissue.

3 Grossman, E B, and Williams, J R, Jr. Relation of Age to Renal Pressor Substance, Arch Int Med, to be published.

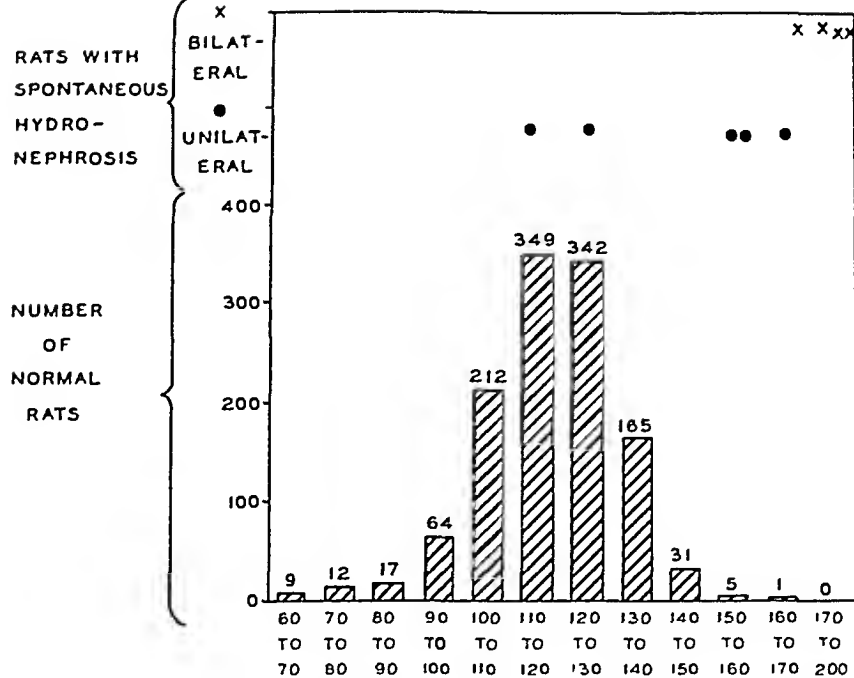


Chart 1—A comparison of the blood pressures of 9 rats with spontaneous hydronephrosis with those of 1,207 normal rats. The figure illustrates the occurrence of hypertension in each of 4 rats with bilateral hydronephrosis and in 3 of 5 rats with unilateral hydronephrosis.

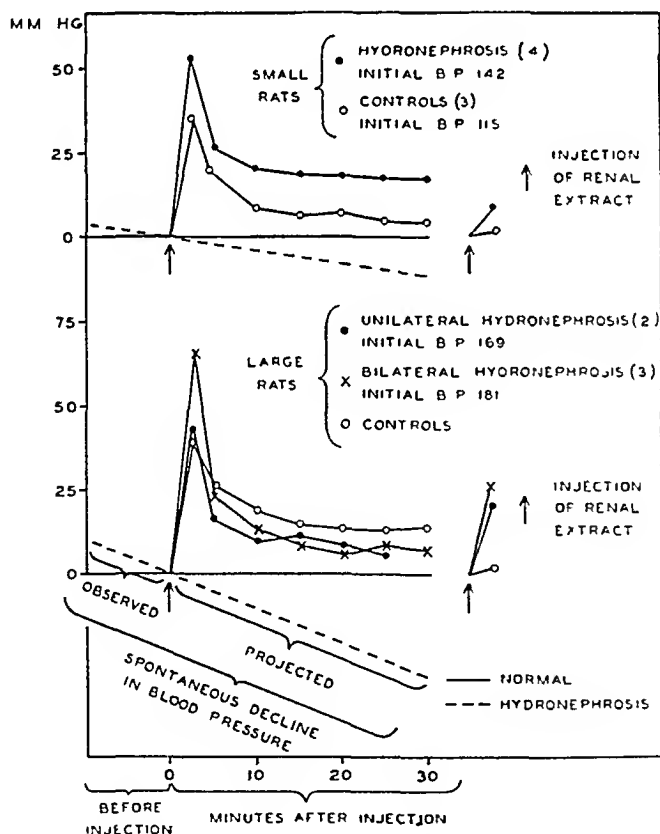


Chart 2—Sensitivity of normal and of hydronephrotic rats to renal pressor substance. The injection of standard renal extract caused a greater initial rise in blood pressure in hydronephrotic than in normal rats. When allowance is made for the tendency of the blood pressure to decline spontaneously, the hydronephrotic animals also seemed to show a more sustained rise in blood pressure. A second injection of renal extract likewise produced a greater response than that which occurred in the control animals. The column of figures to the left shows the rise in mean arterial blood pressure after injection of renal extract.

factor in its sensitivity to renin, it was necessary, for purposes of comparison, to make observations on normal rats of approximately the same size and age as the hydronephrotic animals. Such comparisons are shown in chart 2. It can be seen that the initial rise in blood pressure was greater in the hydronephrotic than that in the normal rats. In the case of the small rats, with only slight elevation of blood pressure, the rise tended to be sustained for a longer time than it was in the controls. However, in the case of the larger rats, with more marked elevation of blood pressure, the rate of decline after the initial injection was more rapid in the controls. This rapid decline may have been an artefact, however, for, as has been pointed out, the hydronephrotic rats with well marked hypertension tended to show a spontaneous decrease in blood pressure. At the time of the injection of renal pressor substance their blood pressure was not constant but was slowly declining. Projection of the curves of their apparent rates of decline (the dotted lines in chart 2) suggests that actually these animals tended to display not only a greater initial rise in blood pressure but also a more sustained rise than did the normal controls. Furthermore, a second injection of renal pressor substance produced a distinctly greater rise in blood pressure in the hydronephrotic animals. The experiments indicate, we believe, that hydronephrotic rats are more sensitive than normal animals to renal extract.

The Pressor Effect of Saline Extracts of Hydronephrotic and of Normal Kidneys—Chart 3 *A* shows a comparison of the responses produced in 3 normal rats by the injection of the extract of kidneys from animals with bilateral hydronephrosis with the effects produced in 3 other normal rats by the injection of extract of the kidneys from normal rats. The extract of the hydronephrotic kidneys caused a somewhat greater initial rise and a markedly greater sustained rise. Chart 3 *B* to *D* shows three comparisons of the saline extract of normal and that of hydronephrotic kidneys from the same rats. In each instance the extract of the diseased kidneys caused a greater rise in blood pressure. The experiments indicate clearly, we believe, that extract of hydronephrotic kidneys of hypertensive rats causes a greater pressor effect when injected into normal rats than does extract of normal kidneys.

Observations Made After Ureteral Ligation—In order to determine whether the changes noted in animals with spontaneous hydronephrosis would occur when hydronephrosis was artificially produced, observations were made after ureteral ligation. It was found that slight but definite hydronephrosis developed within forty-eight hours. In the first experiment both ureters were ligated in 2 rats. Two days later the aorta was cannulated. One of the animals died during the operation. The remaining animal was compared with 3 normal rats as

regards sensitivity to renin. This animal displayed a somewhat greater initial response and a markedly greater sustained response than did any of the controls (chart 4)

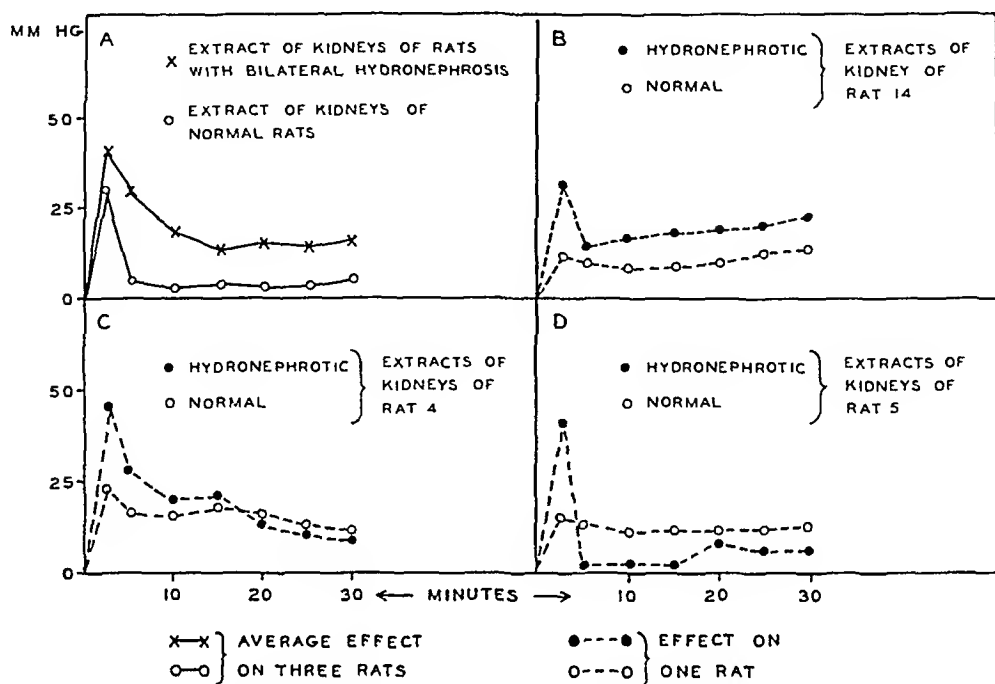


Chart 3—Effect of saline extracts of normal and of hydronephrotic kidneys on the blood pressure of normal rats. Extract of hydronephrotic kidneys had a greater pressor effect than did extract of normal kidneys. The column of figures to the left shows the rise in mean arterial blood pressure.

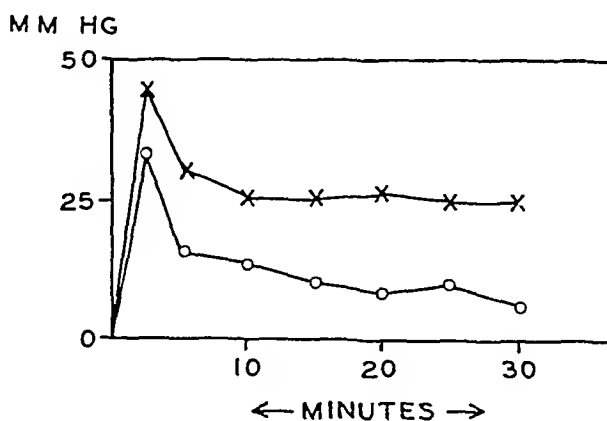


Chart 4—Sensitivity of rats to renal pressor substances. The rat with both ureters ligated (the line with crosses indicates the values) displayed a greater response to standard renal extract than did the controls (the line with circles indicates the average values for 3 normal rats). The figures to the left show the rise in mean arterial blood pressure after injection of renal extract.

In order to avoid the complicating factor of uremia, observations were made after ligation of one ureter, the sensitivity of the animals

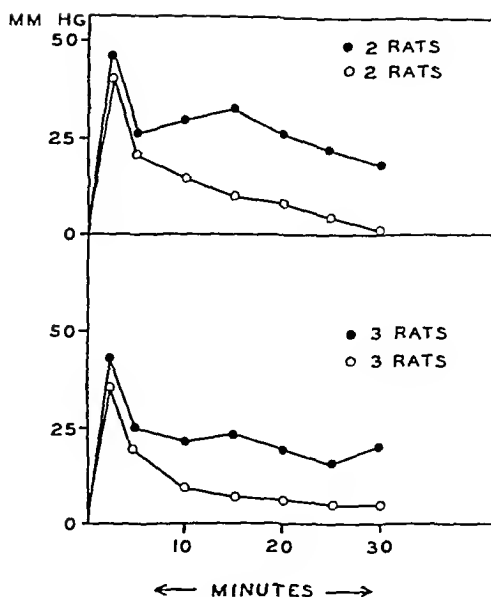


Chart 5—Comparison of the sensitivity of normal rats (white circles) and that of rats with one ureter ligated (black circles) to renal pressor substance. Unilateral ureteral ligation caused increased sensitivity to renal pressor substance. The column of figures to the left shows the rise in mean arterial blood pressure after injection of renal extract.

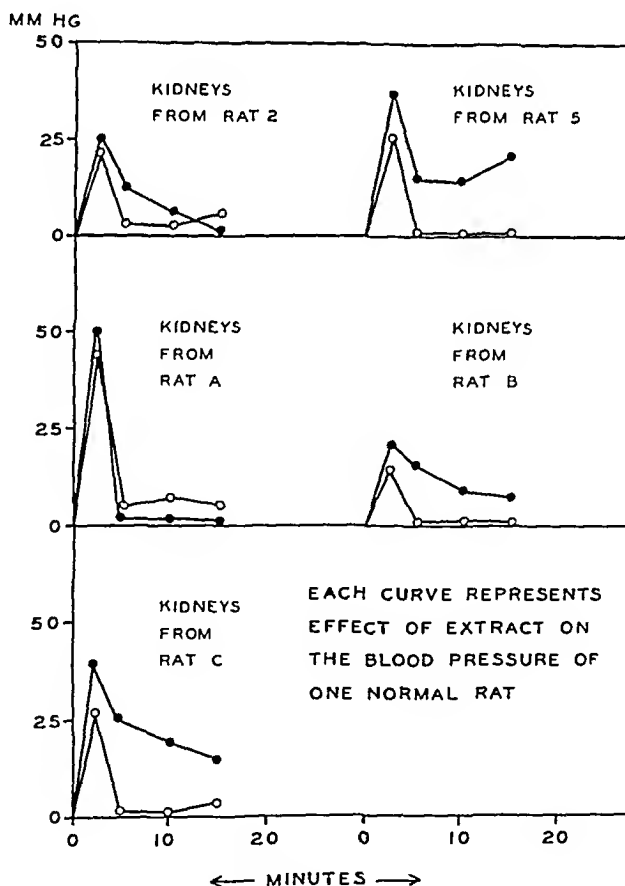


Chart 6—Effects of saline extract of the normal (white circles) and that of the kidney with a ligated ureter (black circles) from the same rat on the blood pressure of normal rats. The extract of the abnormal kidney tended to have a greater pressor effect than did the extract of the opposite normal kidney. The column of figures to the left shows the rise in mean arterial blood pressure.

being determined two days later for one series of rats and four days later for another series. Both series of animals showed a slightly greater initial response to renin and a much more sustained rise in blood pressure than did the controls (chart 5). The average blood pressure of 2 rats after ligation of both ureters was 138 mm of mercury. The average of 5 rats each with one ureter ligated was 122 mm, and that of 8 control animals was 127 mm.

Comparisons were made between the pressor effect of the saline extract of the normal and that of the obstructed kidney of the same rat in 5 instances. In each case the immediate pressor effect obtained from the kidney with a ligated ureter was somewhat greater than that produced by the extract of the normal kidney of the same animal. The abnormal kidney also produced a somewhat more prolonged pressor effect⁴ (chart 6).

COMMENT

The data which have been reported indicate that rats with spontaneous hydronephrosis and rats with hydronephrosis induced by ureteral ligation are more sensitive than untreated rats of similar age and size to the injection of renal extract. They also show that extract of hydronephrotic kidneys, when injected into normal rats, tends to cause a greater pressor effect than does a similar extract of normal kidneys.

Our observations do not make it clear whether the most important factor is increased production in a hydronephrotic kidney of renal pressor substance or increased sensitivity of the rat to this substance. Perhaps both mechanisms are concerned. These cannot be the sole factors, however, for most of the rats with spontaneous hydronephrosis of only one kidney displayed hypertension, while animals with one ureter ligated, although showing increased sensitivity to renin and an increased amount of pressor substance in their kidneys, had no elevation of blood pressure. Apparently the duration of hydronephrosis is a factor of importance in determining whether or not hypertension occurs. Whether the hypertension displayed by the rats with spontaneous hydronephrosis was actually the result of increased formation of renal pressor substance or of heightened sensitivity to this substance is uncertain.

SUMMARY

Rats with spontaneous bilateral hydronephrosis display well marked elevation of blood pressure. Rats with spontaneous unilateral hydronephrosis may or may not have an elevated blood pressure. Hydio-

4 In several preliminary experiments it was found that the pressor effect of the fresh saline extract tended to change markedly after the material had stood in the room for several hours. Consequently, in these experiments the kidneys of a given rat were removed, ground and centrifuged, and the extract was injected immediately.

nephrotic rats respond to the injection of renal extract with a more marked rise in blood pressure than do normal rats of similar size and age. Extract of the abnormal kidneys of rats with spontaneous unilateral hydronephrosis produces greater pressor effects than does a similar extract of the normal kidneys of the same rats. Extract of the kidneys of rats with spontaneous bilateral hydronephrosis causes a greater rise in blood pressure than does extract of the kidneys of normal rats.

Ligation of one ureter for a period of several days causes slight hydronephrosis but no constant rise in blood pressure. After unilateral ureteral ligation the sensitivity of rats to renal pressor substance is somewhat greater than that of normal animals. Extract of the kidney rendered hydronephrotic by ligation of the ureter has a greater pressor effect than does a similar extract of the opposite normal kidney of the same animal.

FATAL ANAPHYLACTIC SHOCK IN MAN

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AND

HERBERT J SCHATTENBERG, M D

NEW ORLEANS

Complications arising from the injection of foreign proteins in man are relatively uncommon, sudden death following their administration may occur, but this is fortunately rare. Park¹ has estimated that fatal reactions due to serum therapy may take place once in 70,000 cases. The cases of fatal anaphylactic shock in man reported in the literature are few, and those in which an autopsy report is given are much less frequent. We feel, therefore, that the report of a fatal case with a pathologic study will be of interest, especially since our observations are similar to those described in cases of so-called thymic death.

REPORT OF A CASE

M M, a Negress aged 39 years, was admitted to the hospital on May 27, 1937. About seven weeks before admission to the hospital she awoke one morning with stiffness of the joints. She was unable to raise her hands to her head and had considerable difficulty in walking. She stated that for the first four days of her illness she had some fever but since then had had a normal temperature. However, she still had some stiffness of the joints at the time of admission to the hospital. Her past history was essentially unimportant. No history of allergy was elicited.

Physical examination revealed a poorly developed and poorly nourished Negress who appeared chronically ill. The blood pressure was 132 systolic and 90 diastolic. The temperature and pulse rate were normal. The pupils were equal and reacted to light and in accommodation. The conjunctivas were pale. The nose, ears and mouth were normal. The neck and thorax showed no abnormality. The lungs were clear. The heart was within normal limits. The rhythm was regular, and a soft systolic murmur, which was not transmitted, was heard at the apex. The abdomen revealed no abnormality. She had some difficulty in moving her joints. The reflexes were all present and normal but were somewhat diminished.

The urine was normal, and a Wassermann test of the blood gave a negative reaction. Roentgen examination of the joints showed atrophic changes.

It was decided to treat the patient's arthritis with foreign protein therapy. On May 29, 1 minim (0.06 cc) of typhoid vaccine was given intravenously. She

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1 Park, W H. Is Serum Anaphylaxis a Danger of Sufficient Importance to Limit Our Use of Protective Sera in the Treatment or Prevention of Diseases? *Tr A Am Physicians* 28 95, 1913, *Antitoxin in Diphtheria*, *J A M A* 76 109 (Jan 8) 1921.

reacted to this with a rise in temperature to 101.8 F, by the next day the temperature was down to normal. On June 3, 2½ minims (0.15 cc) of typhoid vaccine was given intravenously. After this treatment she told the intern that she had free motion in the joints and that in general she felt much better. About thirty minutes after receiving the injection, while sitting on the edge of the bed, she suddenly complained of feeling ill and called for aid. By the time the nurse reached her side, the pulse was imperceptible, and death occurred shortly thereafter.

Autopsy—The body was that of an underdeveloped and undernourished Negress about 40 years of age, weighing approximately 110 pounds (50 Kg) and measuring 165 cm in length. Moderate postmortem rigidity was present. The skin was dark brown and hung rather loosely owing to the loss of subcutaneous tissue. The joints showed no external abnormality. No other changes were noted on external inspection.

The heart weighed 325 Gm. The epicardium was smooth and glistening, and occasional petechiae could be seen beneath it. The right auricle and ventricle were markedly distended with blood, and the myocardium of the right ventricle was somewhat flabby. The left auricle and ventricle contained a few postmortem clots, and their walls were somewhat decreased in consistency. The valves and the endocardium were normal. The coronary vessels were patent throughout. The aorta showed an occasional atheromatous plaque.

The thymus gland appeared small and atrophic.

The lungs were gray and voluminous. The right lung weighed 475 Gm and the left lung 350 Gm. Throughout the pleural surfaces, petechiae could be seen. When the pleural cavities were opened there was no evidence of collapse of the lungs. The lungs were moderately emphysematous, especially around their borders. The posterior portions of the lower lobes of both lungs were somewhat increased in consistency, and their cut surfaces showed some congestion. The rest of the lung tissue was well aerated. The mediastinal lymph nodes were enlarged and soft and showed some deposit of coal pigment.

The mesenteric vessels were congested. The spleen weighed 125 Gm. The capsule was blue, and the consistency of the organ was decreased. On section the parenchyma was pinkish red, and the malpighian corpuscles were prominent. The liver weighed 1,425 Gm, and the capsule was smooth and transparent. The consistency of the organ was decreased, and the cut surface showed marked congestion. The right kidney weighed 145 Gm and the left kidney 155 Gm. The capsules were thin and stripped with ease, leaving a smooth cortical surface. The cut surfaces showed no distortion of the architecture, but considerable congestion was present. The gastrointestinal tract was markedly congested. The lymphoid follicles throughout the tract, but especially in the rectum, were prominent. The lymph nodes in the mesentery of the small intestine and along the abdominal aorta were enlarged, gray and soft.

The pancreas, adrenal glands, gallbladder, urinary bladder and genital organs were grossly normal.

The vessels of the dura, sinuses and surfaces of the brain were markedly congested. The leptomeninges were smooth and glistening. The gyri were not flattened, and the sulci were wide and deep. The cut surfaces of the brain showed some congestion.

Microscopic Observations In different microscopic fields of the sections of the lungs varying changes could be seen. In many instances the alveoli were of normal size, while the alveolar capillaries showed a moderate degree of dilatation. In other portions of the sections these capillaries were engorged with blood, and the alveoli were flattened (fig 1A). No areas of complete collapse of the

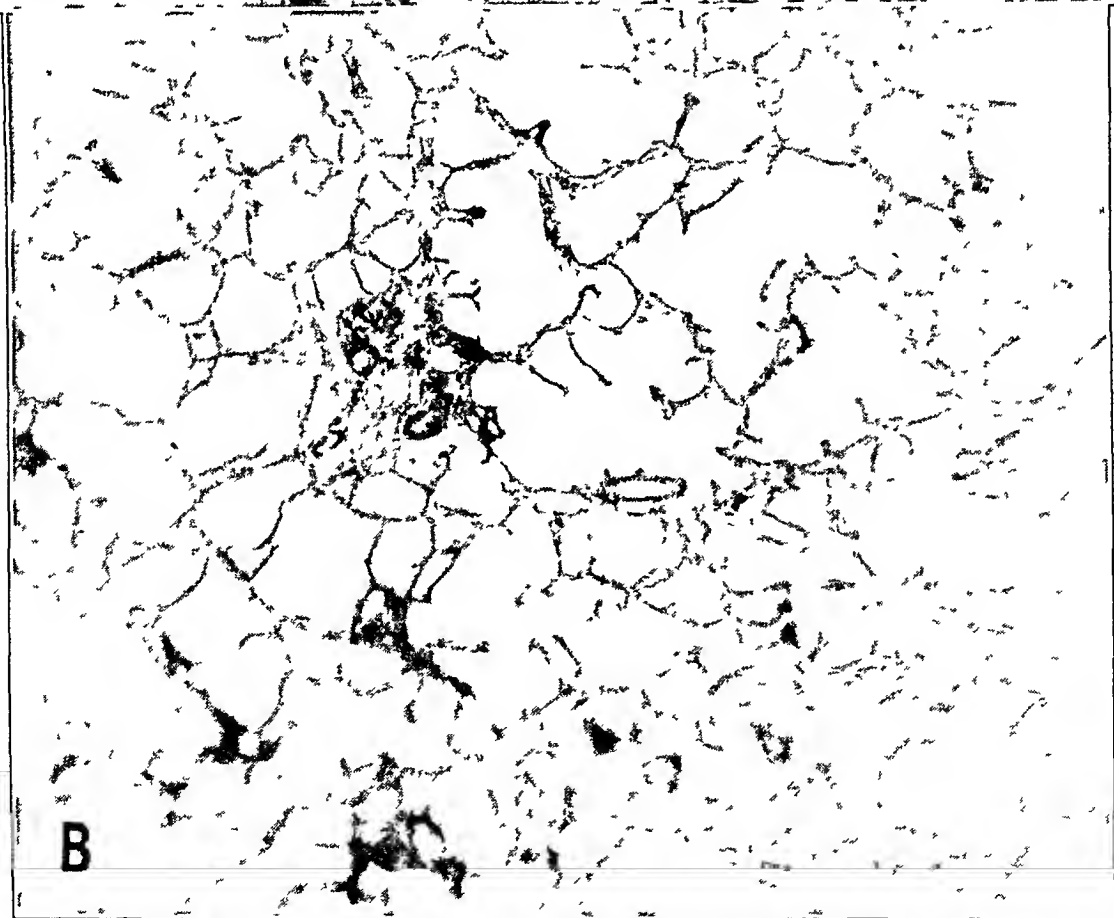
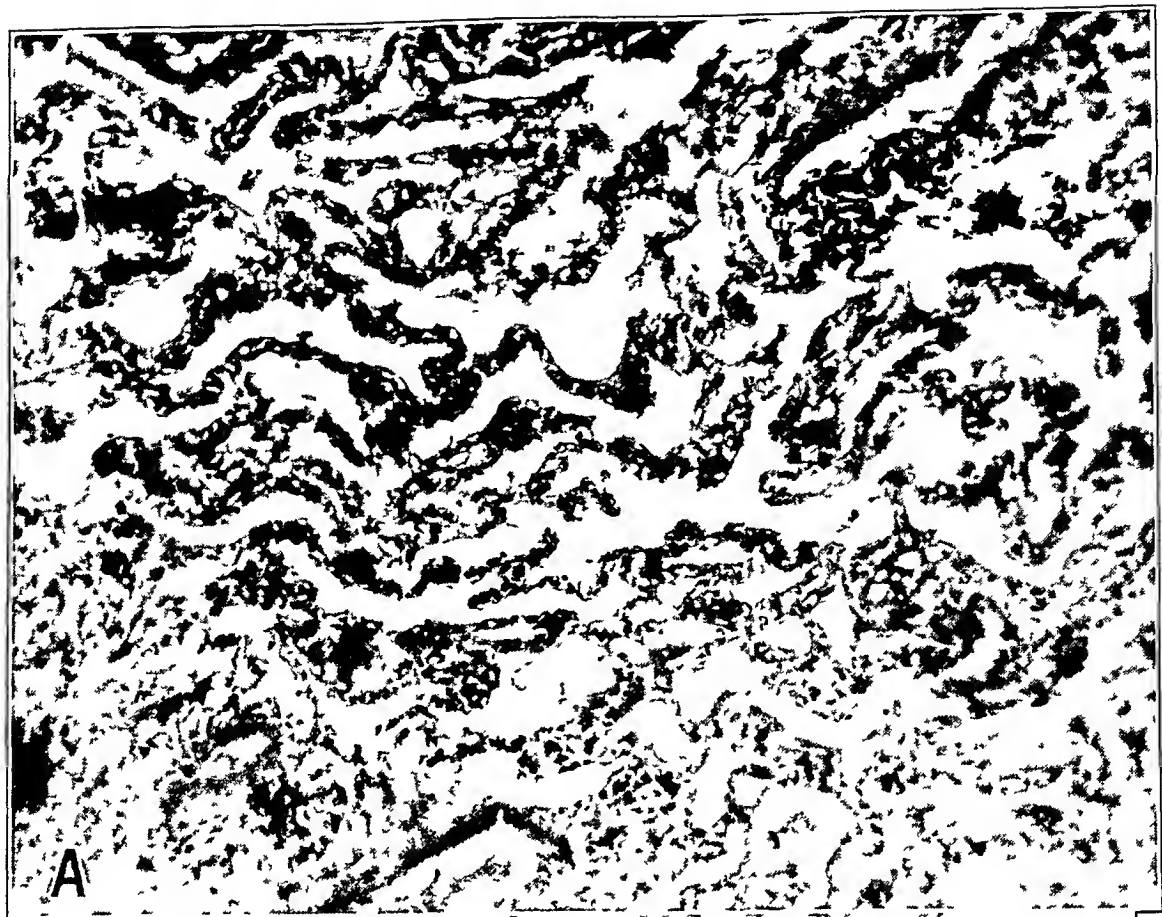


Fig 1—*A*, section of the lung showing compressed alveoli with congested capillaries. *B*, section of the lung showing dilated alveoli and ruptured alveolar walls.

alveoli were noted. Areas were also seen where the alveoli were dilated, and in some instances their walls were ruptured (fig 1 *B*). Here and there, areas were seen where the alveoli were filled with serum, some red blood cells and an occasional leukocyte. Other alveoli were noted which contained some large mononuclear cells and a few leukocytes. Throughout the lungs the capillaries were dilated, but this was least so in the walls of the distended alveoli. Many of the capillaries contained a moderate number of leukocytes, and among these an occasional eosinophil could be seen. Some arterial walls were slightly thickened, and a few arteries were noted which were filled with many leukocytes, mainly neutrophils, with an occasional eosinophil (fig 2). The epithelium lining a few



Fig 2—A pulmonary artery filled with many neutrophils and an occasional eosinophil

bronchioles was arranged in fairly deep folds, and the lumen was slightly narrowed. Numerous small lymphocytic accumulations were seen in the peribronchial tissues throughout the sections.

The sinusoids of the liver were considerably dilated. They were engorged with blood and contained a moderate number of leukocytes (fig 3 *A*). The distribution of the leukocytes was uneven, in that they were found in greater numbers in the sinusoids about the portal canals. The central veins were dilated and congested with red blood cells and some leukocytes. Examination of the leukocytes within the sinusoids revealed a number of mononuclear leukocytes, a moderate number of neutrophils and an occasional eosinophil (fig 3 *B*). The branches of



Fig 3—*A*, section of the liver showing engorged sinusoids *B*, a view under higher power of hepatic sinusoids showing numerous leukocytes

the portal vein were also congested with red blood cells and an occasional leukocyte. The Kupffer cells appeared somewhat enlarged and were separated from the adjacent hepatic cells. The hepatic cells were enlarged, and their cytoplasm was granular and in some areas vacuolated. Some of the nuclei were large and clear, while others were homogeneously dark. A considerable amount of yellow pigment was seen within the hepatic cells, especially the Kupffer cells.

The splenic pulp showed moderate congestion with red blood cells. The malpighian corpuscles were markedly enlarged and had large germinal centers (fig 4). There was no excess of neutrophils within the splenic pulp.

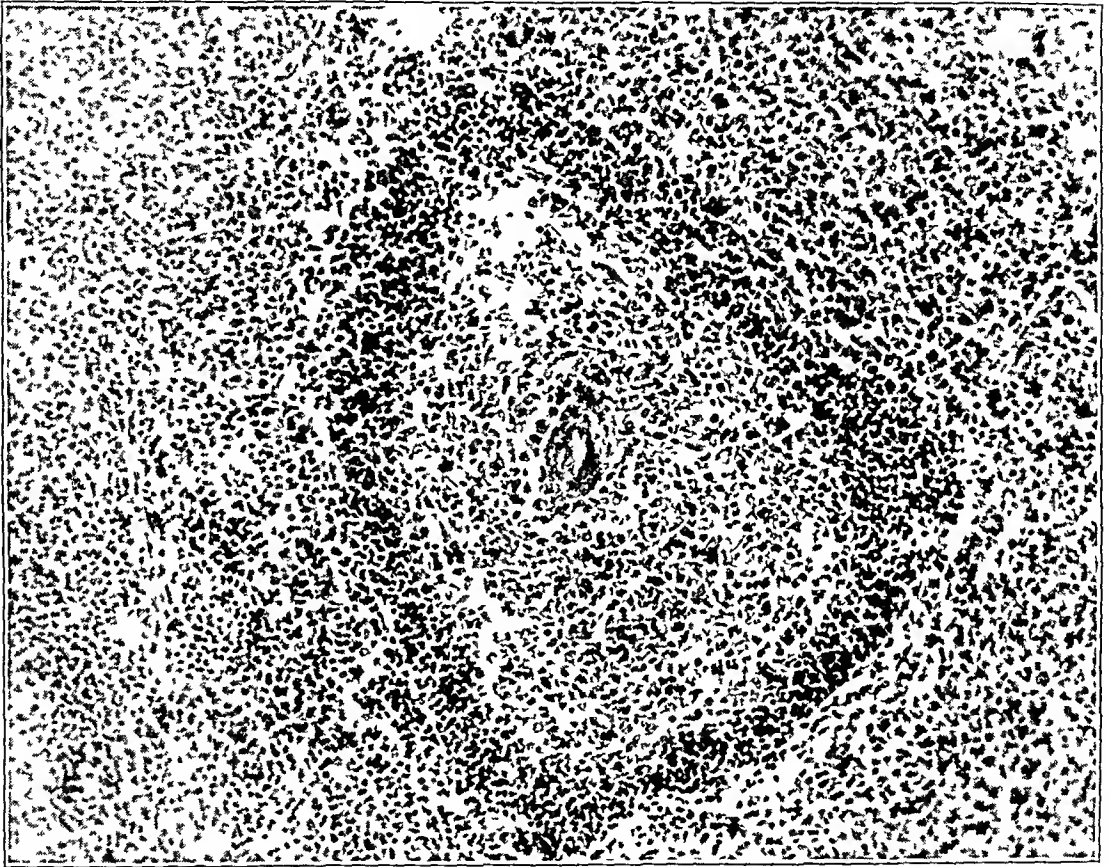


Fig 4—A splenic corpuscle with a large germinal center

The myofibrils of the heart revealed no abnormal changes. The cross striations were well preserved. The blood vessels were slightly dilated and congested with red blood cells and an occasional leukocyte.

In the kidneys an occasional hyalinized glomerular tuft was noted. The capillaries, arteries and veins were all dilated and congested with red blood cells. The tubular cells showed no pathologic changes.

The glandular epithelium of the rectum was normal. All the blood vessels were dilated and congested with red blood cells and an occasional leukocyte. The lymphoid follicles were markedly enlarged.

Sections from the brain, adrenal glands, pancreas, thymus and lymph nodes showed marked congestion of the blood vessels.

COMMENT

The anatomic changes observed in our case agree in many respects with those observed in some animals² and in human beings³ after anaphylactic death. However, postmortem observations reported in the literature on sudden death following injection of a foreign protein show no marked constancy. Such changes as emphysema with bronchiolar contraction and thickening of the arterioles of the lung, dilatation of the right side of the heart, congestion of the liver and other internal organs and enlargement of the thymus have been reported in various cases.

Much experimental work has been done on anaphylaxis in animals. The symptoms of acute anaphylactic shock vary markedly in the different species of animals and depend largely on a difference in the underlying pathologic changes occurring in the respective species. The difference depends on the location of the "shock organ" or "tissue." In the guinea pig the tissue acted on is the bronchial musculature, which contracts and causes death by asphyxia. The "shock tissue" in the rabbit is the muscle of the pulmonary artery and death occurs as a result of the cessation of the pulmonary circulation because of mechanical interference. In the dog the liver is the important "shock organ," and death is brought about by the sudden accumulation of most of the animal's blood in the liver and abdominal veins as a result of obstruction to the circulation in the hepatic vein. This obstruction is due to contraction of the musculature of the vein or to swelling of the capillary endothelium, but which is the more important factor has not been definitely established. That the former is more important is the view held by most investigators. This phenomenon causes marked lowering of the systemic blood pressure, and this is further depressed by the action of hepatogenous substances on the systemic terminal vessels, causing their dilatation.

Much of the work on anaphylaxis in dogs has been done by Weil.² The changes that he observed were similar to those noted in the case herein reported. It seems likely that the cause of death in this case was due to a fall in blood pressure caused by dilatation of the sinusoids of the liver and of the abdominal veins and possibly of the capillaries of the lung. This drop in blood pressure caused anoxemia of the respiratory centers in the medulla with cessation of respiratory movements, and cardiac failure. The collection of leukocytes in the liver and lung may be related to the leukopenia of the peripheral blood observed in cases of anaphylactic shock, and the eosinophils noted suggest an allergic background.

² Weil, R. Studies in Anaphylaxis. XXI Anaphylaxis in Dogs, a Study of the Liver in Shock and in Peptone Poisoning, *J. Immunol.* **2**: 525, 1917.

³ Dean, H. R. The Histology of a Case of Anaphylactic Shock Occurring in a Man, *J. Path. & Bact.* **25**: 305, 1922.

Cases have been reported of fatal anaphylactic shock in man in which the mechanism was that of the "guinea pig type,"⁴ namely, bronchiolospasm with respiratory failure. It may therefore be assumed that the mechanism in man may vary in different cases, being of one of at least two types, either the bronchiolospastic or the splanchnic type.

Waldbott⁵ has made some interesting observations concerning the relation between anaphylaxis and status lymphaticus. He studied a number of cases in which the diagnosis of "thymic death" had been made and observed uniform changes in the lungs, namely, edematous, hemorrhagic areas in the alveoli, emphysema alternating with atelectasis and occasional eosinophilic cells. These changes were similar to those reported in the literature in many cases of fatal anaphylactic shock in man. He observed similar changes in the lungs of infants with true allergic asthma. Waldbott and Anthony⁶ have noted, further, that in children with enlargement of the thymus, true allergic asthma develops later in life. Waldbott⁷ has suggested that "thymic death" may be a preallergic phenomenon which is probably identical with anaphylactic shock, as the body has not yet set up a sufficient defensive mechanism against the invading antigen, the patient therefore dies suddenly instead of having an asthmatic attack.

SUMMARY

A case of fatal anaphylactic shock following the second intravenous injection of a foreign protein is reported, with necropsy observations.

The gross pathologic changes were marked congestion of the liver and more moderate congestion of the other organs. General enlargement of the lymph nodes and a persistent thymus gland were also noted.

The significant microscopic changes were dilatation and congestion of the hepatic sinusoids and the alveolar capillaries of the lungs. There was an apparent relative increase in the leukocytes and the eosinophils within these vessels. The alveoli were compressed in some areas and dilated in others, and in some instances their walls were ruptured. The malpighian corpuscles of the spleen were increased in size and had large germinal centers.

It is suggested that the mechanism of death in this case was of the so-called "dog" type, namely, capillary dilation, especially of the liver, with a corresponding fall in blood pressure and cardiac failure.

4 Sheppe, W. M. Fatal Anaphylaxis in Man, *J. Lab. & Clin. Med.* **16** 372, 1931.

5 Waldbott, G. L. So-Called "Thymic Death" VI. The Pathologic Process in Thirty-Four Cases, *Am. J. Dis. Child.* **47** 41 (Jan.) 1934.

6 Waldbott, G. L., and Anthony, G. E. So-Called Thymic Hyperplasia IV. A Follow-Up Study of Thirty Cases, *Am. J. Dis. Child.* **47** 34 (Jan.) 1934.

7 Waldbott, G. L. The Allergic Theory of So-Called Thymic Death, *J. A. M. A.* **105** 657 (Aug. 31) 1935.

CORONARY OCCLUSION WITH AND WITHOUT PAIN

ANALYSIS OF ONE HUNDRED CASES IN WHICH AUTOPSY WAS DONE
WITH REFERENCE TO THE TENSION FACTOR IN CARDIAC PAIN

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In the early years of the clinical recognition of coronary occlusion, substernal or epigastric pain of at least several hours' duration was considered to be a characteristic feature. Subsequent observations have shown not only that this type of pain may be closely simulated by other conditions, such as acute surgical disorders of the abdomen, pulmonary embolism, dissecting aneurysm of the aorta, interstitial emphysema and pneumothorax, but also that painless occlusion of the coronary artery may occur in a certain number of cases, with dyspnea replacing pain most frequently as the presenting symptom. The clinical picture here is that of failure of the left ventricle, followed by congestive heart failure. In a still smaller percentage of cases the severe initial anginal pain may be replaced by symptoms suggesting a cerebral vascular lesion, such as sudden weakness, dizziness, syncope and unconsciousness, or by gastrointestinal features, such as nausea, vomiting, distention, obstipation and abdominal pain. The rather high incidence of cardiac infarction without pain is not, however, generally recognized. Recently the number of published reports dealing with this fact has been increasing. White,¹ for example, has emphasized the importance of the nonpainful features of coronary occlusion, and the rather frequent occurrence of cardiac infarcts without pain is evidenced by numerous case reports.² To our knowledge, few reports of large series

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1 White, S M. Non-Painful Features of Coronary Occlusion, *Ann Int Med* 8: 690-700, 1934.

2 (a) Barnes, A R. Acute Coronary Occlusion Without the Characteristic History of Anginal Pain. Course, Treatment and Electrocardiographic Findings, *M Clin North America* 18: 477-489, 1934. (b) Bramwell, C. British Medical Association Lecture on Coronary Occlusion, *Brit M J* 1: 681-685, 1930. (c) East, C F T, Bain, C W C, and Cary, F L. Cardiac Infarction Without Pain,

(Footnote continued on next page)

of cases with autopsy data have thus far been published in which this particular point is considered. Wearn,³ for instance, reported that in 53 per cent of 19 cases, the diagnosis being confirmed by necropsy, there was absence of pain. In a series of 76 cases, with autopsy performed in 53 cases, Davis⁴ found pain present in 21 cases (40 per cent) and absent in 21 cases (40 per cent), sudden death preventing the recording of an adequate history regarding pain in 11 others. If these cases are excluded, painless occlusion occurred in 50 per cent of this series. Recently Bruenn, Turner and Levy⁵ concluded from a clinicopathologic study of 476 cases of disease of the coronary arteries that the incidence of cardiac pain varies, depending on the type and the location of the fundamental lesion. Thus 12 (39 per cent) of a group of 31 patients with proved thrombosis had pain, and 19 (61 per cent) did not. Katz and his associates⁶ reported that there was no history of pain in 13 of a group of 34 cases in which the heart was examined post mortem, an incidence of 38 per cent. Kennedy,⁷ in a recent communication, suggested that the occurrence of coronary thrombosis without any painful or uncomfortable sensations is by no means as common as has been described in the foregoing reports. In a series of 200 cases in which there were 109 old and 142 recent infarcts, he found, after excluding 48 cases because of unsatisfactory histories, that "Ninety-one per cent of the recent and 64 per cent of the old infarcts had the classical pain of a coronary attack."

Lancet **2** 60-63, 1928 (d) Herrmann, G. R. Synopsis of Diseases of the Heart and Arteries, St. Louis, C. V. Mosby Company, 1936, p. 214. (e) Parkinson, J., and Bedford, D. E. Cardiac Infarction and Coronary Thrombosis, Lancet **1** 4-11, 1928. (f) Smith, H. L., and Brink, J. R. Acute Coronary Thrombosis Without Characteristic Pain and Without Symptoms of Shock, Minnesota Med **19** 346-349, 1936. (g) Stenn, F. Painless Coronary Occlusion, Illinois M. J. **67** 381-382, 1935. (h) Menard, O. J., and Hurxthal, L. M. Painless Coronary Thrombosis as a Post-Operative Complication, S. Clin. North America **11** 395-401, 1931. (i) Boyd, L. J., and Warblow, C. W. Coronary Thrombosis Without Pain, Am. J. M. Sc. **194** 814-824, 1937.

3 Wearn, J. T. Thrombosis of the Coronary Arteries with Infarction of the Heart, Am. J. M. Sc. **165** 250-276, 1923.

4 Davis, N. S., III. Coronary Thrombosis Without Pain. Its Incidence and Pathology, J. A. M. A. **98** 1806 (May 21) 1932.

5 Bruenn, H. G., Turner, K. B., and Levy, R. L. Notes on Cardiac Pain and Coronary Disease. Correlation of Observations Made During Life with Structural Changes Found at Autopsy in Four Hundred and Seventy-Six Cases, Am. Heart J. **11** 34-40, 1936.

6 Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N. Coronary Arteriosclerosis, Coronary Thrombosis, and the Resulting Myocardial Changes, Am. Heart J. **10** 567-595 and 762-792, 1935.

7 Kennedy, J. A. The Incidence of Myocardial Infarction Without Pain in Two Hundred Autopsied Cases, Am. Heart J. **14** 703-709, 1937.

Our own clinical impression that painless closure of the coronary artery was not infrequent has been confirmed by an analysis of a series of 100 cases in which autopsy was performed. The generally accepted theories of cardiac pain do not offer a completely satisfactory explanation, in our opinion, for the presence of pain in some instances of cardiac infarction and its absence in others. The present study was undertaken, therefore, in order to correlate the clinical and the pathologic data in a large series of proved cases, with the hope that some light might be shed on the factors concerned in this problem.

CLINICOPATHOLOGIC STUDY

The patients included in this analysis were drawn from the medical service of the Albany Hospital and from the private services of a number of our associates.⁸ The complete pathologic reports, made by members of the department of pathology of the Albany Medical College, were placed at our disposal by Prof. A. W. Wright. During the years 1917 to 1937, 3,040 postmortem examinations were performed in this department, and the diagnosis of coronary thrombosis or cardiac infarction was made in 140 instances (4.6 per cent). We have used the term coronary occlusion because it is more comprehensive. It includes obstruction of the coronary artery due to thrombosis, fibrotic narrowing and embolism. The result of such obstruction is a cardiac infarct, provided sufficient time elapses before death for its development. The case histories of these 140 patients were carefully reviewed, together with the autopsy protocols, and the primary cause of death was established in each case. This procedure resulted in the elimination of 40 cases for the following reasons: (1) 8 examples of the focal or embolic type of scarring in the myocardium with infarcts less than 1 cm. in diameter, (2) 25 instances of old or recent cardiac infarction in which death was due clearly to some other pathologic condition, such as pneumonia, peritonitis, postoperative shock, fracture of the skull, cerebral hemorrhage, multiple pulmonary infarcts, advanced pulmonary tuberculosis, carcinoma of the prostate, diabetic coma, uremia, septicemia or pneumococcal meningitis, and (3) 7 instances of sudden death due to cardiac infarction in which records of the history, physical examination or medical observation before death were lacking. This left a group of 100 patients, coronary occlusion being the primary cause of death in 80 instances, a definitely contributory cause in 15 and a probable cause in 5. Gross infarcts, measuring more than 1 cm. in diameter, with palpable areas of softening or fibrosis in the myocardium, were present

⁸ The following physicians gave us permission to include their cases in this study: Drs. G. E. Beilby, K. E. Crounse, J. L. Donhauser, A. W. Elting, F. N. Guyer, J. L. Hemstead, H. H. Hun, F. B. Maguire, C. E. Martin, Thomas Ordway, A. H. Traver, J. A. Sampson, A. H. Stein, C. K. Winne Jr. and L. H. Ziegler.

in all except 2 cases, in which the thrombosis of the coronary artery had apparently been too recent for infarction to occur. Pulmonary infarcts secondary to cardiac infarction were found in 15 instances. There was only 1 case of true syphilitic aortitis in the series with actual destruction of the media of the arterial wall. There were 2 examples of old rheumatic heart disease, with superimposed arteriosclerotic heart disease. There was 1 instance of periarteritis nodosa. Arteriosclerotic changes in the coronary arteries of the same general nature were present in the entire series, with the exception of the aforementioned case of periarteritis nodosa. It was not possible to separate sharply the cases of hypertensive cardiovascular disease with marked

TABLE 1—*Analysis of Clinical Findings for One Hundred Patients with Coronary Occlusion with Cardiac Infarction*

Division of Patients	Age		Sex		History of Preceding Attacks of Cardiac Pain		Dyspnea as an Outstanding Symptom		History of Hypertension		Pericardial Friction Rub	
	No. of Patients											
	Decades		Males	Females	Positive	Negative	Present	Absent	Positive	Negative	Present	Absent
Group 1	31-40	2	1	1								
53 patients	41-50	4	3	1	35	23						
with cardiac	51-60	25	21	4			9	49				
infarction	61-70	18	12	6					21	37		
with pain	71-80	9	5	4							7	51
	81-90	0	0	0								
Percentage					60	40	15	85	36	64	12	88
Group 2	31-40	1*	1*	0	8	34						
42 patients	41-50	3	3	0			26	16				
with cardiac	51-60	9	8	1					7	35		
infarction	61-70	14	7	7								
without pain	71-80	12	7	5							1	41
	81-90	3	2	1								
Percentage		100	70	30	19	81	62	38	17	83	2	98

* One patient had periarteritis nodosa.

coronary sclerosis from those of pure arteriosclerotic heart disease with changes in the coronary arteries but no hypertension. Most of the patients were admitted to the hospital with a falling or low blood pressure.

For the purpose of analysis these 100 patients were divided into two groups: (1) those who had cardiac pain in the final attack and (2) those who did not. Certain pertinent clinical facts were then correlated with the postmortem reports, and the results are summarized in tables 1 and 2. In the first group were included all patients who complained of pain even of minimal degree in the substernal, precordial or epigastric region, as well as in the shoulders, arms, wrists, jaws or scapulas. Vague discomfort or a sense of pressure or constriction in the chest was not recorded as pain. No systematic study was made of the relative sensitivity to painful stimuli of the patients in these

TABLE 2—Analysis of Postmortem Data for One Hundred Patients with Coronary Occlusion with Cardiac Infarction

Division of Patients	Description of Infarct				Location of Infarct						Acute Pericarditis		Cardiac Rupture with Hemopericardium		Thrombosis of Coronary Artery		Degree of Coronary Sclerosis	
	Acute	Old	Acute and Old	Absent	Anterior Apical	Midventricular	Posterior Basal	Anterior Apical, and Midventricular	Anterior Apical, Midventricular and Posterior Basal	Present	Absent	Present	Absent	Present	Absent	Mild to Moderate	Marked	
Group 1 58 patients with cardiac infarction with pain	20	11	26	1	39	2	4	3	2	7	29	6	52	33	25	13	45	
Percentage	35	19	46		67					43	50*			57	43	22	78	
Group 2 42 patients with cardiac infarction without pain	5	18	18	1	26	3	7	0	0	5	29	3	39	13	29	5	37†	
Percentage	12	41	44		62					10	69†			31	69	12	88	

* Four patients (7 per cent) had chronic adhesive pericarditis

† One patient had periarthritis nodosa

‡ Five patients (12 per cent) had chronic adhesive pericarditis

two groups Although such differences, as pointed out by Libman,⁹ undoubtedly exist, it is to be noted that several of the patients who died in a painless attack of coronary occlusion had been previously seen by us when they complained of severe pain because of other conditions, such as herpes zoster, tabes dorsalis and carbuncle Furthermore, it seems probable that although the severity of cardiac pain may be definitely less in some hyposensitive patients, it would not be safe to assume that this reduced sensitivity could alone explain the complete absence of cardiac pain in certain fatal attacks of coronary occlusion In addition to this, 19 per cent of the patients included in the second group, as will be described later, gave a history of definite anginal pain previous to the final fatal attack

INCIDENCE, AGE AND SEX

In our series of 100 patients with coronary occlusion, 42 suffered fatal attacks which were unaccompanied by pain, while the remaining 58 complained of cardiac pain of varying location, intensity and duration It is to be noted that 30 of the 40 patients excluded for the reasons previously indicated did not have pain Had these been included in the series the percentage of cases of painless infarcts would have been considerably greater In 66 per cent of the cases death occurred between the fiftieth and the seventieth year Males apparently tended to die about a decade earlier than females, the peak mortality for the former being reached at approximately 55 years and for the latter at 65 years (chart 1) Of the 58 patients who died in a painful attack of coronary occlusion, 43 (74 per cent) succumbed between the ages of 50 and 70, while of the 42 patients who died without pain, 23 (55 per cent) succumbed in the sixth and seventh decades For the more advanced decades, aged 70 to 90, painful occlusion occurred in 9 of 58 patients (16 per cent) and painless occlusion in 15 of 42 patients (36 per cent) Thus it appears that painful attacks tend to occur somewhat more frequently in the earlier decades (51 to 70 years) and that painless seizures show a higher incidence in the advanced decades (71 to 90 years, chart 2) Males experienced their fatal and painful coronary occlusion ten years earlier than did females (chart 3) The same relation between the sexes existed in the group with painless attacks (chart 4)

HISTORY OF PRECEDING ATTACKS

In studying the past histories of the 58 patients in group 1, who died in a painful attack, it was interesting to find that 35 (60 per cent) had been the subject of one or two previous painful seizures and 23

⁹ Libman, E Observations on Individual Sensitiveness to Pain, *J A M A* 102 335-341 (Feb 3) 1934

(40 per cent) had never before suffered from severe stenocardia¹⁰ Of the 42 patients comprising group 2, who died in a painless attack, there was a history of preceding anginal pain for only 8 (19 per cent), with no record of its occurrence in 34 (81 per cent) It seems that if

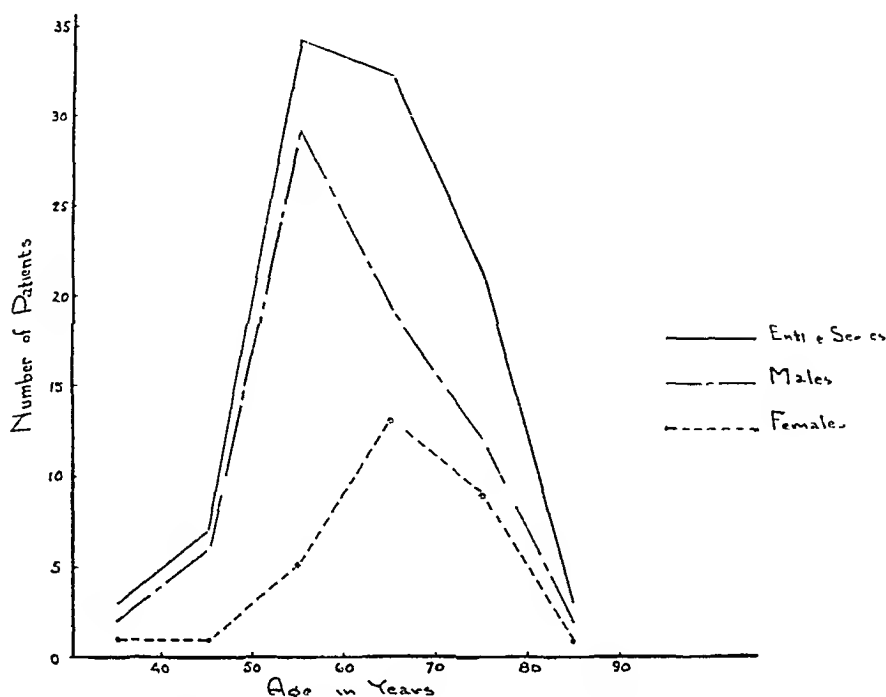


Chart 1—Age-sex correlation in 100 cases of coronary occlusion

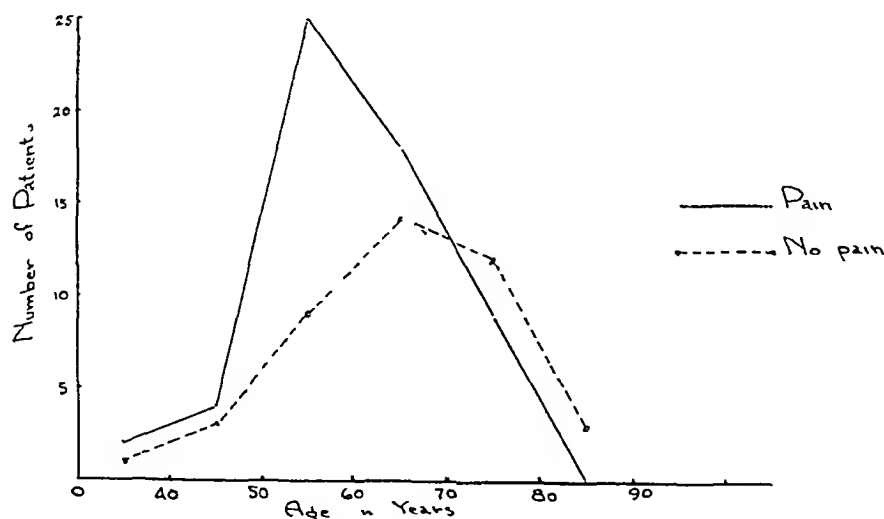


Chart 2—Age-sex correlation of painful and painless coronary occlusion

a patient with progressive disease of the coronary arteries has one or more attacks of severe substernal pain and recovers, he is more likely

¹⁰ It was not possible to conclude whether the pain was that of coronary occlusion or of angina pectoris in many cases

than not to suffer pain in his last or fatal attack. On the other hand, if advancing disease of the coronary arteries manifests itself only by dyspnea and diminishing cardiac function, the patient so afflicted is more prone to die with a painless cardiac infarct. This deduction is similar to that of Bruenn and his associates,⁵ who reported that in their experience the patients who had no symptoms prior to the acute episode were most likely not to have pain associated with it.

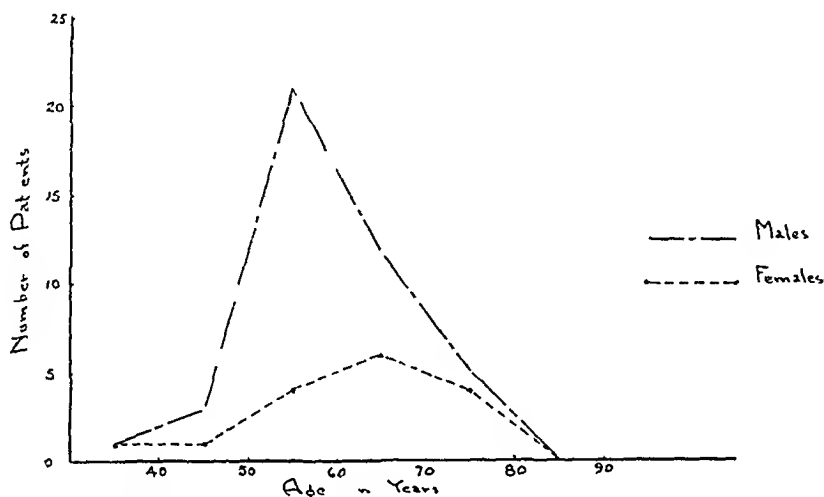


Chart 3—Age-sex distribution in 58 cases of painful coronary occlusion

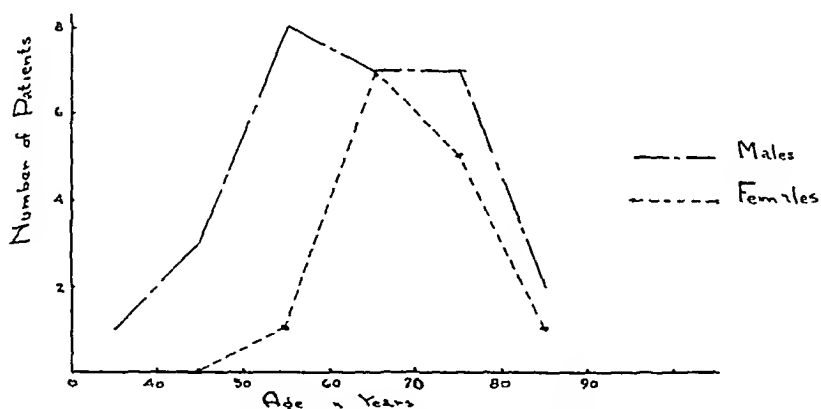


Chart 4—Age-sex distribution in 42 cases of painless coronary occlusion

DYSYPNEA

Dyspnea was the outstanding symptom of only 9 (15 per cent) of the 58 patients in group 1 (patients with painful occlusion). In contrast with this, dyspnea, although often present in the remaining 49 patients (85 per cent) of this group, was overshadowed by pain. In group 2, comprising 42 patients with painless occlusion, there were 26 instances (62 per cent) in which dyspnea was the dominant symp-

tom In 16 cases (38 per cent) dyspnea when present was of minor degree From this evidence one may see that when pain occurs in cardiac infarction this symptom overshadows dyspnea in more than four fifths of the cases Conversely, it is clear that in coronary closure unaccompanied by pain, dyspnea becomes a rather prominent and outstanding symptom in approximately two thirds of the cases This observation is in accord with that originally made by Obrastzow and Straschesko,¹¹ who stated that dyspnea may be the pain equivalent

HYPERTENSION

In group 1 there were 21 patients (36 per cent) with a history of preceding hypertension, while in group 2 there were only 7 (17 per cent) Of a total of 28 patients in the two groups with a history of preceding hypertension, 21 (75 per cent) had pain accompanying coronary occlusion It appears that previous hypertension is about three times more frequent in the group of patients who had painful attacks

PERICARDIAL FRICTION RUB

A pericardial friction rub was heard in 7 patients (12 per cent) belonging to group 1 and in 1 patient (2 per cent) in group 2 Of a total of 8 instances in which audible friction was recorded, 7 (88 per cent) occurred in patients with painful occlusion (group 1) Although the evanescent nature of this clinical sign is fully appreciated, it appears to be decidedly more common in patients experiencing painful cardiac infarction

TYPE OF INFARCTION

The 98 patients¹² were divided into three classes, viz, class A, those showing recent or acute infarcts, class B, those presenting old or healed infarcts, and class C, those having both acute and old infarction In group 1, comprising 57 patients with painful coronary occlusion, there were 20 with acute infarcts (35 per cent), 11 with old infarcts (19 per cent) and 26 (46 per cent) with combined acute and old infarcts Combining classes A and B, one finds that acute infarction was present actually in 46 of the 57 patients (81 per cent) in group 1 and old infarction in only 11 patients (19 per cent)

In group 2, including 41 patients with painless coronary occlusion, there were 5 (12 per cent) with acute, 18 (44 per cent) with old healed infarcts and 18 (44 per cent) with the combined type of infarct (acute and old) Combining classes A and C, it is seen that 23 patients

11 Obrastzow, W P, and Straschesko, N D Zur Kenntnis der Thrombose der Koronararterien des Herzens, *Ztschr f klin Med* **71** 115-132, 1910

12 Two patients did not have a gross infarct, death occurring before it developed

(56 per cent), or slightly over half of those in group 2, had acute infarction but in spite of this did not experience pain

Viewed in another way, of the total of 69 patients with actual acute infarction in the entire series, two-thirds were in group 1 and one-third in group 2. Of 29 patients with old infarcts, however, approximately two-thirds fell in group 2 and one-third in group 1. Thus it appears that while acute infarcts tend to be accompanied by pain and old ones do not, there must still be some other factor conditioning the production of pain in coronary occlusion. Kennedy,⁷ as previously stated, found in a series of 200 cases that pain was more frequently present with recent than with old infarcts.

LOCATION OF INFARCT

Cardiac infarcts were present most frequently in the anterior apical region. The incidence of infarction located in this area in the patients with painful attacks and in those without them was almost identical: group 1, 39 patients (67 per cent), group 2, 26 patients (62 per cent). The location of the infarct in this region therefore appears to bear no relation to the presence or absence of pain. With regard to the other sites of infarction, i. e., the midventricular and posterior basal regions of the heart, there were too few cases for analysis. Likewise, no conclusions could be drawn from the 17 cases in which infarcts were present in two or three sites. Bruenn and his associates⁸ found no causal relation between pain and the particular artery or branch occluded.

Opinion is apparently divided on the question of the relative frequency of the occurrence of infarcts in the anterior apical, midventricular and posterior basal regions of the heart. One group of authors¹³ have reported that in the large majority of their cases the apical portion of the left ventricle was involved, while another group¹⁴ have reported that the midventricular and posterior basal regions taken together were the site of the lesion in over half the cases.

ACUTE PERICARDITIS

In group 1 there were 22 patients (38 per cent) with acute pericarditis, 4 with chronic pericarditis, 3 with both acute and chronic pericarditis and 29 with no pericarditis. In group 2 there were 5

13 Levine, S. A. Coronary Thrombosis. Its Various Clinical Features, Medicine Monograph, Baltimore, Williams & Wilkins Company, 1929, vol. 16. Gorham, L. W., Ordway, T., Jacobsen, V. C., and Hosoi, K. The Pathology of Cardiac Infarction, *Tr. Am. Climat. & Clin. A.* **48**: 105-113, 1932.

14 Barnes, A. R., and Ball, R. G. Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Post-Mortem Examinations, *Am. J. M. Sc.* **183**: 215-225, 1932. Parkinson and Bedford^{2e}

patients with acute pericarditis, 5 with chronic pericarditis, 3 with acute and chronic pericarditis and 29 with no evidence of pericarditis. Acute pericarditis was present in 43 per cent of the patients in group 1 and in only 19 per cent of those in group 2. Of a total of 33 instances of acute pericarditis, 25 (75 per cent) occurred in patients in group 1. It is evident that acute pericarditis is commonly present in painful coronary occlusion and often absent in the painless attacks, but it is equally apparent that this fact alone does not explain the presence or absence of pain.

CARDIAC RUPTURE WITH HEMOPERICARDIUM

Cardiac rupture with hemopericardium occurred in 9 patients in the series of 100, 6 belonging in group 1 and 3 in group 2. The total number of patients is too small to permit one to draw definite conclusions. Cardiac rupture, however, does not seem to have any significant bearing on the presence of pain in coronary occlusion.

THROMBOSIS OF THE CORONARY ARTERY

In group 1, 33 of the 58 patients with painful attacks (approximately 57 per cent) showed at autopsy thrombosis of a coronary artery. Among 42 patients in group 2, who were without pain, thrombosis occurred in 13 instances (31 per cent). If the total number of patients in groups 1 and 2 who showed actual thrombosis are considered, it is found that in 33 of the 46 patients (72 per cent) the thrombosis was characterized by pain and that in 13 (28 per cent) it was not. This suggests that thrombosis per se when present in a coronary artery carries with it a two and a half to one chance of causing a painful seizure. The reverse of this, however, is not true, i. e., that absence of actual thrombosis means probable absence of pain. Of 54 patients in the two groups with no evidence of thrombosis, pain was present in 25 (46 per cent) and absent in 29 (54 per cent). Although actual acute thrombosis favors the occurrence of pain, absence of it by no means excludes the possibility of pain. It is reasonable therefore to suppose that there is still another factor besides thrombosis on which the initiation of cardiac pain depends. Biuenn, Turner and Levy³ stated "It was only when the vessel was actually occluded, either by the arteriosclerotic process or by thrombosis, that the incidence of pain doubled." These authors did not mention the exact incidence of pain in cases of thrombosis alone.

CORONARY SCLEROSIS

Sclerosis of the coronary arteries was present in varying degree in every case of our series, even in the 2 instances of rheumatic and 1 of

syphilitic heart disease From the gross and microscopic descriptions of the vessels it was found possible to estimate roughly the amount of coronary sclerosis present in each case, grading it as mild, moderate or marked The patient with periarteritis nodosa showed typical involvement of the coronary vessels It was described as follows in the autopsy protocol

The coronary arteries had an unusual appearance On the anterior surface of the branches which emerge from the auriculoventricular margin were seen many small translucent spherical enlargements of their walls, so that the vessels appeared to have a series of small beads or nodules A few of the vessels on the posterior surface also showed this unusual condition

Microscopically the most striking changes in the heart were seen in the coronary vessels The arterial walls were greatly enlarged, owing to the proliferation of young fibrous tissue in the intima, reducing the lumens to slits or obstructing them entirely The periarterial tissue showed many young fibroblasts and was rich in capillaries Other vessels showed organizing thrombi, in some instances the thrombi being infiltrated with many lymphocytes The coronary arteries were thus the seat of a process typical of periarteritis nodosa

This rather unusual case was included in the series because it answered the criterion as to the size of infarct used in selection, there being a small recent infarct at the apex of the left ventricle, measuring about 1 cm in diameter, with a mural thrombus beneath it The walls of the larger vessels were thickened, but no thrombosis was present on gross examination The high incidence of pain in the presence of actual thrombosis plus acute infarction will be discussed later At this point it may be noted that there was no pain in this case, although an acute infarct was present and thrombi were seen in the small vessels under the microscope Small infarcts, even though recent, when due to microscopic thrombi probably do not cause pain, possibly because the smaller arteries are almost devoid of sensory nerves

In group 1, 13 patients (22 per cent) showed a mild to moderate degree of coronary sclerosis, and 45 (78 per cent) showed marked sclerosis In group 2, moderate involvement was noted in only 5 patients (12 per cent) and advanced coronary sclerosis in 37 (88 per cent) Of 18 patients in the two groups showing only a mild or moderate degree of coronary sclerosis, 13 (72 per cent) suffered from pain, and 5 (28 per cent) did not Of a total of 82 patients showing marked coronary sclerosis, 37 (45 per cent) did not have pain, as against 45 (55 per cent) who did show this symptom Thus pain seems to occur more frequently in the presence of a mild or moderate degree of vascular sclerosis than it does in the advanced stages With maximal grades of sclerosis, pain may be present or absent in approximately an equal number of cases One cannot draw any definite deductions from these figures other than to state that the presence or absence of pain does not directly vary with the degree of sclerosis

Although some of the factors which have been discussed seem to bear a definite relation to the pain of coronary occlusion, no single one is found which offers a complete explanation of the mechanism of pain production. However, as will be shown later, the action of a combination of several of these factors sheds more light on this problem.

COMMENT

Clinical interest in the origin of cardiac pain may properly be said to have begun with the classic observation of William Harvey, who showed his sovereign, Charles I, that the heart itself is "without a sense of touch"¹⁵. The demonstration was made on a man whose thoracic wall had been partially removed by accident. After the first correct clinical diagnosis of cardiac infarction, by Hammer,¹⁶ the excellent thesis of Marie¹⁷ and the description of the syndrome by Obrastzow and Straschesko,¹¹ there appeared the first comprehensive study of the disease in this country, by Herrick.¹⁸ Since 1912 numerous American observers have established the various clinical features of this condition, emphasizing severe precordial, substernal or epigastric pain as a cardinal feature. In recent years there has been a gradual, although not general, recognition of the fact that coronary occlusion is often unassociated with pain. Isolated case reports do not afford an index as to the actual frequency. The published reports of groups of cases bearing on this point place the incidence at from 38 to 61 per cent. Of our series of 100 patients studied post mortem, painless coronary occlusion occurred in 42 per cent.

From the preceding analysis one can roughly visualize two main types of coronary disease which lead to cardiac infarction. The first type, present in a somewhat larger group of patients than the other, is characterized clinically by painful seizures, tending to occur somewhat earlier in life and bearing no sexual preference except that the peak mortality is reached a decade sooner in males than in females. The patients afflicted with pain are more likely to have a previous history of stenocardia, preceding hypertension is more common, dyspnea is usually overshadowed in severity by pain and a pericardial friction rub is much more frequent. At autopsy this group of patients is

15 Harvey, W. *The Works of William Harvey*, translated by R. Willis, London, Sydenham Society, 1847, p. 383.

16 Hammer, A. Ein Fall von thrombotischen Verschluss einer der Kranzarterien des Herzens, *Wien med Wchnschr* 28:97-102, 1878.

17 Marie, R. *L'infarctus du myocarde et ses conséquences*, Thesis, Paris, no. 88, 1896.

18 Herrick, J. B. Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* 59:2015 (Dec. 7) 1912.

more likely than the other group to show acute infarction of the heart, acute pericarditis and actual thrombosis of a larger coronary vessel. The location of the infarct and the occurrence of hemopericardium due to rupture of the ventricle have no relation to pain. Painful infarcts are more likely to occur in the presence of mild or moderate sclerosis than are painless ones.

The second group of patients, somewhat smaller than the first, show clinical absence of cardiac pain. Attacks tend to occur later in life, with no relation to sex except that males appear to die a decade earlier than females. Preceding thoracic pain and hypertension are less common than in the first group, while dyspnea is more often a dominant symptom. A pericardial friction rub is rarely heard in cases of painless occlusion. At autopsy the hearts of these patients tend to show old infarcts, absence of acute pericarditis and relatively fewer instances of thrombosis of the coronary arteries. The location of the infarct and the presence of hemopericardium secondary to ventricular rupture bear no relation to the absence of pain. This group of patients shows relatively few instances of mild or moderate sclerosis of the coronary arteries. Marked sclerosis is about as frequent in this group as in the first.

It is evident that no single factor of those analyzed will enable one accurately to differentiate the painful from the painless type of coronary occlusion. Our study does suggest, however, that in the first group of patients, with painful occlusion, one is dealing with a rather more acute process in which relatively sudden obstruction of a coronary artery by (1) a thrombus tends to result in (2) acute cardiac infarction and (3) acute pericarditis. If one reviews the entire series of 100 cases with the idea of discovering a combination of factors, rather than a single one, which bear a more direct relation to pain, it is found that 15 patients showed actual thrombosis accompanied by acute infarction and that 10 of these also had acute pericarditis. Every one of these 15 patients had painful occlusion. On the other hand, our study suggests that painless coronary occlusion represents a more gradually developing pathologic process, in which (1) the progressive narrowing of the artery results from fibrosis rather than from actual thrombosis, and that this in turn appears to lead as a rule to (2) old fibrous infarcts with (3) rather infrequent acute pericarditis. In the entire series there were 17 patients with old cardiac infarcts who had no record of thrombosis or of acute pericarditis. Twelve of these 17 patients (70 per cent) did not have pain, while 5 (30 per cent) did show this symptom. It is possible that 1 or more of the 5 patients who had pain may have had thrombi in the vessels which were not discovered. It is well recognized⁶ that thrombi in the coronary arteries may be overlooked unless numerous cross sections are made and the vessels are

carefully examined. Reexamination of hearts already studied proves that, in spite of reasonable care, this lesion may be missed. Furthermore the pain suffered by all these patients was relatively mild, and dyspnea was an outstanding symptom in 4 of them.

If one again refers to table 2, with the thought that perhaps a combination of factors rather than a single one may bear some more definite relation to cardiac pain, one finds the following interesting facts:

1. The 5 patients with acute infarction unaccompanied by pain showed no evidence of thrombosis.

2. Six of the 11 patients with old infarction accompanied by pain revealed either acute pericarditis or thrombosis. The remaining 5 patients with old infarction and with pain may have had thrombi which were overlooked. Furthermore, pain was of slight degree in every instance and was overshadowed by dyspnea in 4.

3. Of 8 patients with acute pericarditis without pain, 6 showed no thrombosis while the other 2 had marked sclerosis of the coronary arteries.

4. In each of the 13 patients with painless occlusion with actual thrombosis, marked sclerosis was present.

5. Twenty of the 25 patients with painful occlusion without thrombosis showed acute infarction or acute pericarditis. The 5 remaining patients with pain but no thrombosis were the same 5 with old infarction mentioned under paragraph 2. Actual thrombosis may have been present in some of these cases and the pain of mild degree was overshadowed by dyspnea in 4 of them.

6. In each of the 5 patients with painless occlusion with mild or moderate sclerosis there was absence of thrombosis.

THEORETIC CONSIDERATIONS

The manner in which cardiac pain is initiated in coronary occlusion has been explained in various ways as reviewed in detail by Sutton,¹⁹ Katz²⁰ and Wiggers.²¹ Of the several explanations the theory most widely accepted today is that of Lewis²² who advanced the idea that the pain is dependent on myocardial ischemia. He stated that impairment of the coronary circulation results in disturbance of the nutrition

19 Sutton, D. C. Cardiac Pain, *J. A. M. A.* 97:1369-1370 (Nov. 7) 1931.

20 Katz, L. N. Mechanism of Pain Production in Angina Pectoris. *Am. Heart J.* 10:322-327, 1935.

21 Wiggers, C. J. The Physiology of Cardiac Pain. In Levy, R. L. *Disease of the Coronary Arteries and Cardiac Pain*. New York, The Macmillan Company, 1936, chap. 6, pp. 163-180.

22 Lewis, T. Pain in Muscular Ischemia. Its Relation to Anginal Pain, *Arch. Int. Med.* 49:713-727 (May) 1932.

of the cardiac muscle and the rapid development of an unknown chemical "P substance" which acts as a pain-producing stimulus to the nerve endings. This theory has been supported by Herrick,²³ who has explained one of its most obvious defects, viz., its failure adequately to account for the absence of pain in a large percentage of cases, even though extreme grades of ischemia are present. He has stated that in gradually progressive coronary sclerosis, ischemia may result in an area that is "relatively anesthetized by destruction of vessels, nerve and functioning muscle, so that a painful response to the new obstruction is lacking." The final complete obstruction comes without a sudden shock, the element of surprise is lacking as the heart is in a sense prepared for the supreme insult."

It is well known that the cardiac muscle itself is insensitive to pain on mechanical stimulation and that the afferent sensory fibers which do respond to such stimuli lie in the adventitial layers of the coronary arteries and send terminal branches at intervals to the smooth muscle fibers of the arterial coat, the richness of the nerve supply increasing toward the base of the heart.²⁴ In any discussion of cardiac pain this fact is of prime importance. The fundamental question is whether the sympathetic nerve endings in the blood vessels are stimulated by a chemical substance resulting from ischemia alone or whether they may also respond to pure mechanical stimulation. The source of the pain in either case is in the wall of the coronary vessel and not in the cardiac muscle *per se*. It seems logical to suppose, therefore, that sclerotic changes in the coronary arteries must bear some direct relation to the presence and absence of pain in coronary occlusion. One might further suppose that early atheromatous changes in the walls of the coronary arteries render the afferent nerve endings hypersensitive to painful stimuli, so that slight changes in the tension within the affected vessels would produce pain just as readily as would a hypothetical chemical substance. Further, it is conceivable that advanced sclerosis of the coronary vessels may lead to actual degeneration of the nerve endings in the vascular wall or that stiffening of the arterial coat and loss of elasticity may reach a point at which a sudden change in tension is no longer an adequate stimulus to the production of pain. Whether the stimulus is chemical or mechanical, however, pain must be initiated by a factor acting on the sensory nerves in the adventitial or muscular coats of the coronary arteries.

23 Herrick, J. B. Coronary Artery in Health and Disease, *Am Heart J* 6 589-607, 1931

24 Katz, L. N., Mayne, W., and Weinstein, W. Cardiac Pain. The Presence of Pain Fibers in the Nerve Plexus Surrounding the Coronary Vessels, *Arch Int Med* 55 760-772 (May) 1935. Moore, R. M., and Singleton, A. O., Jr. Peripheral Course of Pain Fibers Supplying Coronary Arteries and the Myocardium. *Proc Soc Exper Biol & Med* 32 1492-1494, 1935.

From a physiologic point of view it is logical to believe that afferent nerve fibers of blood vessels may respond to mechanical as well as to chemical stimuli. In a normal blood vessel, occlusion of the lumen is accompanied by pain, provided the distention of the wall of the vessel is sufficient to reach the threshold level of pain. If the obstruction is sudden the pain may be intense. Embolism of the femoral artery, e g., after operation, is generally attended by severe pain, but gradual fibrotic narrowing of the same artery leading to marked ischemia may occur without pain. Dissecting aneurysm of the aorta is characterized by excruciating pain, which is directly associated with the stretching and tearing of the arterial wall. By analogy there is a strong argument that the mechanical factor of tension is important in the mechanism of pain production in arteries.²⁵ In coronary occlusion it is suggested that pain varies directly with the speed with which increased tension is produced on the wall of the coronary artery proximal to the obstruction and with the pathologic changes in the wall of the vessel, whether these changes are due to reduced elasticity or actual degeneration of the sensory nerves.

The mechanical theory of cardiac pain has been suggested many times in the past, but an imposing majority of physiologists and cardiologists at present favor the explanation of cardiac pain on the basis of ischemia²² or anoxemia.²⁶ The studies of Wenckebach,²⁷ however, and more recently those of other observers submit evidence in support of a mechanical theory. Herrmann²⁴ said "In personal experimental studies I have noted distention of the artery behind the obstruction, and this led me to express the idea that it is the dilatation of the artery and the consequent stretching of its wall, proximal to the obstruction, that causes the stimulation of the nerve plexus about the vessel and the initiation of pain." Allbutt²⁸ concluded that a similar mechanism accounts for cardiac pain by causing tension on the aorta. Against the mechanical theory of cardiac pain, the argument has been advanced that occlusion of a coronary vessel can have no significant effect on the arterial pressure within it.²⁹ While the argument that the tension

25 The work of Bray (Bray, H. A. Tension Theory of Pleuritic Pain, *Am Rev Tuberc* **13**:14-20, 1926) in showing that pleural pain is due not to friction rub but to tension on the nerve endings in the parietal pleura, stimulated our interest in the problem of cardiac pain.

26 Keefer, C. S., and Resnik, W. H. Angina Pectoris. A Syndrome Caused by the Anoxemia of the Myocardium, *Arch Int Med* **41**: 769-807 (June) 1928.

27 Wenckebach, K. F. Toter Punkt, "second Wind," und Angina pectoris, *Wien klin Wchnschr* **41**: 1-6, 1928.

28 Allbutt, T. C. Diseases of the Arteries Including Angina Pectoris, New York, The Macmillan Company, 1915.

29 Wiggers, C. J., and Cotton, F. S. Studies on the Coronary Circulation. I. The Coronary Pressure Pulses and Their Interpretation, *Am J Physiol* **106**: 9-15, 1933.

factor may cause cardiac pain appears physiologically sound, the evidence which we have thus far presented does not disprove Lewis' concept of the role of myocardial ischemia in the production of cardiac pain. Our study does suggest, however, that a mechanical as well as a chemical factor may initiate the pain in coronary occlusion. Further, it affords an apparently reasonable explanation for the total absence of pain in certain cases of cardiac infarction, in which extreme grades of ischemia proved by autopsy are present.

It is fully realized that the factor of tension in the production of cardiac pain must be subjected to carefully controlled experimental studies before its significance can be appreciated. Added evidence of its importance has been obtained by showing that cardiac pain may be produced in animals by tension on the walls of the coronary arteries alone and without a significant disturbance of the circulation of blood in these vessels, or, in other words, that pain may be initiated without ischemia.³⁰

SUMMARY

Study of the clinical histories and necropsy data for 100 patients with proved coronary occlusion showed that 58 had cardiac pain and 42 did not, indicating a higher frequency of painless occlusion than is generally recognized.

The following broad statement may be made regarding group 1, comprising 58 patients who suffered from cardiac pain in a fatal attack. The patients tend to be younger, males show the peak mortality ten years earlier than do females, a history of preceding attacks of anginal pain and of hypertension is more common, pain overshadows dyspnea as a symptom and a pericardial friction rub is much more often heard. Actual thrombosis, acute infarction, acute pericarditis and milder grades of coronary sclerosis are more frequently encountered than in the patients in group 2. The location of the infarct and the rupture of the ventricle, with resulting hemopericardium, bear no relation to pain.

The following general statement may be made regarding group 2, comprising 42 patients who had no pain in a fatal attack of coronary occlusion. The patients tend to be older than those in group 1, males show the peak mortality a decade earlier than do females, a history of preceding attacks of anginal pain and of hypertension is less common, dyspnea is generally an outstanding symptom and a pericardial friction rub is rarely heard. Old infarcts, with absence of actual thrombosis and pericarditis, are more frequent. Marked sclerosis of the coronary

³⁰ Martin, S. J., and Gorham, L. W. Cardiac Pain. An Experimental Study with Reference to the Tension Factor, *Arch Int Med*, this issue, p. 840.

arteries is slightly though not significantly more often encountered. The location of the infarct and the rupture of the ventricular wall, with resulting hemopericardium, bear no direct relation to the absence of pain.

A combination of actual thrombosis of the coronary artery and acute infarction was accompanied by pain in every one of the 15 instances in which these two factors were present. A combination of fibrotic narrowing of a coronary artery, without actual thrombosis, plus old infarction and absence of pericarditis was not accompanied by pain in 12 of 17 patients (70 per cent). All the 5 patients who did have pain suffered from only a slight degree of it, dyspnea was the dominant symptom in 4 of these cases.

The old mechanical theory of cardiac pain advocated by Allbutt and Wenckebach and more recently advocated by Herrmann, which has been generally discarded in favor of Lewis' theory of ischemia, has been reexamined in the light of our study, and the role of a tension factor has been emphasized. Briefly, according to this theory the pain in coronary occlusion varies directly with the speed with which increased tension is produced on the wall of the coronary artery proximal to the obstruction and with the pathologic changes in the wall, whether these changes are due to a reduced elasticity or an actual degeneration of the sensory nerves.

The tension factor seems to offer a reasonable explanation not only for the presence but for the absence of pain in cases of coronary occlusion.

Added support for the importance of the factor of tension in the production of cardiac pain has been obtained by an experimental study on animals, the results of which are recorded in a separate communication.

CARDIAC PAIN

AN EXPERIMENTAL STUDY WITH REFERENCE TO THE TENSION FACTOR

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Cardiac pain has long been of clinical interest, but not until the past decade has it been subjected to laboratory investigation. Although Allbutt's¹ theory of the aortic origin of angina pectoris was once widely accepted, recent experimental evidence strongly points toward the cardiac origin of pain. Sutton and Lueth² have shown that compression by means of a ligature on coronary vessels in the unanesthetized dog results in pain characteristic of angina pectoris. Their studies have been confirmed by White, Garrey and Atkins³ and by Katz and his associates⁴. All these authors have agreed that the fundamental mechanism initiating pain is a chemical factor produced by impaired coronary circulation. In essence, this contention is the basis of Lewis'⁵ theory that myocardial ischemia is the cause of cardiac pain. From the aforementioned studies it is generally inferred that the mechanical factor is of secondary importance in producing cardiac pain.

That the mechanical or tension factor may be of major significance has been expressed by Herrmann⁶ and has been suggested in a recent

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1 Allbutt, T C. Diseases of the Arteries Including Angina Pectoris, New York, The Macmillan Company, 1915

2 Sutton, D C, and Lueth, H C. Pain, Arch Int Med **45** 827-867 (June) 1930

3 White, J C, Garrey, W E, and Atkins, J A. Cardiac Innervation Experimental and Clinical Studies, Arch Surg **26** 765-786 (May) 1933

4 Katz, L N, Mayne, W, and Weinstein, W. Cardiac Pain. The Presence of Pain Fibers in the Nerve Plexus Surrounding the Coronary Vessels, Arch Int Med **55** 760-772 (May) 1935

5 Lewis, T. Pain in Muscular Ischemia. Its Relation to Anginal Pain, Arch Int Med **49** 713-727 (May) 1932

6 Herrmann, G R. Synopsis of Diseases of the Heart and Arteries, St Louis, C V Mosby Company, 1936, p 214

clinicopathologic study of painful and painless coronary occlusion⁷ The following experiments have been performed in an effort to determine the possible importance of a mechanical factor in the initiation of cardiac pain

PROCEDURE

Seven normal adult dogs were prepared under pentobarbital sodium anesthesia and artificial respiration, which are essential according to the procedure of Sutton⁸ The significant modification of this author's technic employed in our experiments was the use of four or five ligatures, instead of one or two, placed as follows In the first animal a black silk ligature was looped through the visceral pericardium and the adventitia of the wall of the anterior descending branch of the left coronary artery on its right side about 2 cm from its aortic opening A second ligature was then similarly introduced into the left side of the wall of the same vessel (fig 1 *A*) Care was taken not to pass the ligatures into the lumen of the vessel In the remaining 6 dogs three ligatures were inserted in like manner, but each was placed approximately 90 degrees from its neighbor and in the same transverse plane (fig 1 *C*) This modification was carried out in order to preserve the coronary blood flow and at the same time to permit the application of tension (fig 1 *D*) In these dogs, in addition, a fourth ligature was passed under the same vessel and through the myocardium about 1.5 cm distal to the initial ligatures, and, finally, a fifth or control ligature was put through the visceral pericardium and myocardium a few centimeters to the right or to the left of the same coronary artery These ligatures were then led to the exterior of the thoracic cage through separate flanged glass tubes that were sewed in place in the parietal pericardium, with the proximal ends of the tubes extending freely into the pericardial cavity (fig 2) In 3 cases a sixth ligature was attached to the parietal pericardium and extended to the surface of the chest The rest of the surgical procedure was completed in the manner previously described,² and the dogs were permitted to recover from the anesthesia

RESULTS

The criteria accepted as signifying the presence of pain in dogs awakening from anesthesia were, in general, similar to those reported by Sutton and Lueth² In order, there occurred in 80 per cent of the observations (1) an initial and rapid increase in heart rate, (2) an initial temporary decrease in the rate of respiration, with marked increase in amplitude, followed by dyspnea and tachypnea, (3) movements of the legs, characteristically first the left foreleg, then the right hindleg and finally all four extremities, (4) extension of the head and neck, and (5) last, a gasping inspiratory whine Salivation was noted in only 33 per cent of the observations No animals were allowed to suffer Application of tension on the coronary ligatures was terminated

7 Gorham, L. W., and Martin, S. J. Coronary Occlusion With and Without Pain. Analysis of One Hundred Cases in Which Autopsy Was Done with Reference to the Tension Factor in Cardiac Pain, *Arch. Int. Med.*, this issue, p. 821

8 Sutton, D. C., and King, W. W. Physiological Effects of Temporary Occlusion of the Coronary Vessels, *Proc. Soc. Exper. Biol. & Med.* **25**: 842-844, 1928. Sutton and Lueth²

as soon as the pain response was noted. In all animals the sensitivity to ordinary painful stimuli on recovery from the anesthesia was determined as a control. The stimuli used consisted of pinching the skin of the groin with a hemostat, passing a needle through the skin and also incising the skin of this area with a scalpel.

A Effect of Tension on the Ligatures in the Coronary Artery—

1 Preliminary tests, made by exerting a steady, firm pull on the ligatures, were performed on all dogs before the parietal pericardium was closed by suture. The results were as follows: (a) Marked tension on any one of ligatures 1 to 4, inclusive (fig 2 *A*), or simultaneously on the lateral ligatures (1 and 2 in dog 1 and 1 and 3 in all others)

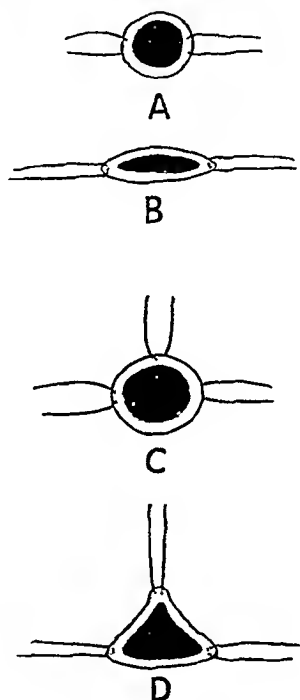


Fig 1—Sketch showing the position of the ligatures in the coronary artery. *A*, the right and left lateral ligatures. *B*, the ligatures are the same as those in *A* except that there is tension on them. *C*, ligatures 1, 2 and 3 are approximately 90 degrees apart and in the same plane. *D*, the ligatures are the same as those in *C* except that there is tension on them.

produced flattening and blanching of the distal portion of the coronary vessel. This compression of the vessel and the resulting pallor of the distal portion of the artery signified not only the satisfactory and secure position of the ligatures but also the probable complete cessation of the coronary blood flow. (b) Moderate or mild tension on these same ligatures caused no change in color or contour of the vessel distally except in the case of ligature 4. In the case of this ligature, which encircled the vessel, the results were uniformly similar to those recorded under *a*, since even mild tension resulted in a marked decrease of blood

flow (c) Mild to marked tension applied equally and simultaneously to ligatures 1, 2 and 3 produced no visible change in either the color or the contour of the vessel distally. It may be reasonably inferred, therefore, that the coronary blood flow was not seriously impaired (fig 1 *D*). (d) Tension of varying degrees on ligature 5 of course had no effect on the coronary artery. It resulted only in elevating a portion of the myocardium and in increasing the heart rate.

2 In the series of dogs used, after recovery from anesthesia, four to six hours later, it was observed that the sensitivity of the skin to painful stimuli varied. The threshold of pain was definitely lowered by the anesthesia, since none responded to pinching of the skin in the groin or the passing of a needle through it. However, all but 1 dog reacted to the stimulus of the cutaneous incision in varying degree,

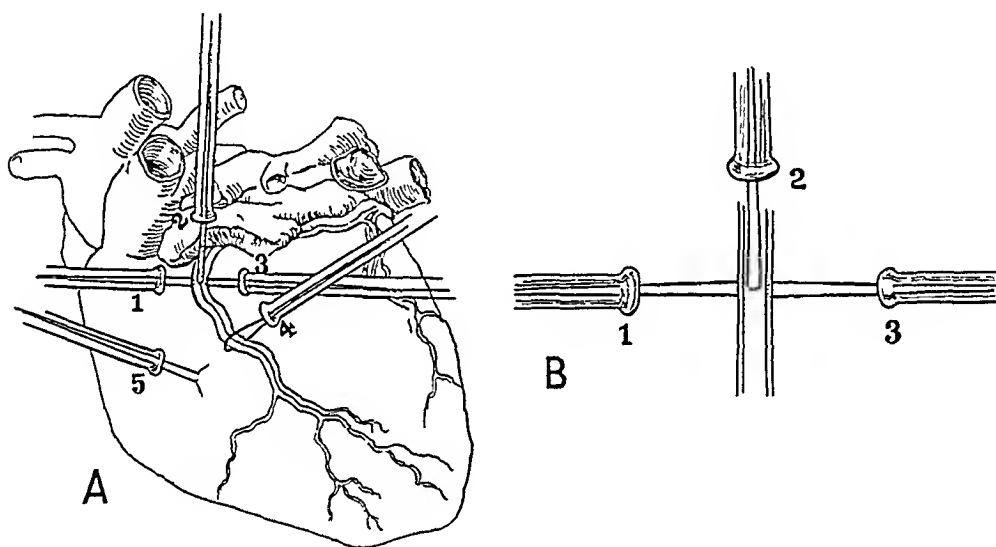


Fig 2—*A* showing five ligatures in place and extending from the heart through flanged tubes. *B*, a diagrammatic representation of the position of coronary ligatures 1, 2 and 3.

characterized chiefly by movement of one or both hindlegs and an increase in the cardiac and respiratory rates. There was no dyspnea. Movement of the forelegs, extension of the head and neck and the gasp-like inspiratory whine, which so definitely characterize pain produced by tension on the coronary vessel, were all absent.

The observations made when tension was applied to the different ligatures are summarized in table 1. It can be readily seen from this table that tension for less than half a minute on any one of ligatures 1 to 4 or on any combination of them initiated cardiac pain in the unanesthetized dog. There was also a notable decrease in the rate of respiration, with a compensatory increase in amplitude. Tension for four minutes on the myocardium and visceral pericardium by means of ligature 5 or, in 3 cases, the ligature on the parietal pericardium produced only a rise in heart rate but none of the significant features

of cardiac pain. This observation confirms previous reports⁹. With reference to respiration, the changes were slight. The onset of pain seemed to occur earliest by the simultaneous pulling of ligatures 1, 2 and 3 and latest on tension of a single ligature. The time required for the return to normal of the cardiac and respiratory rates and for the disappearance of other signs of cardiac pain was significantly prolonged when tension was exerted on ligature 4 (under the coronary vessel). According to the generally accepted theory of ischemia, this may have been due to the time necessary for the removal of the accumulated metabolites resulting from complete coronary occlusion.

TABLE 1—*Summary of Data on the Application of Tension on Ligatures in the Coronary Arteries of Seven Unanesthetized Dogs*

Number of Observations	Ligature Under Tension	Normal*		Tension of Ligatures (Approximately 5 Gm.)					Application of Tension After Change in Heart Rate, Seconds	Average Onset of Pain, Seconds	Average Return to Nor- mal, Seconds
		Heart Rate per Min	Respiratory Rate per Min	Average Increase in Heart Rate per Min	Average Initial Decrease in Respira- tory Rate per Min	Movement of Legs	Extension of Head	Cry†			
38	L ₁ or L ₂ or L ₃	158	38	32 (20-43)	9.0 (6.14)	+	+	++	15.25	35 (30-44)	51 (39-62)
27	L ₁ and L ₃	166	40	28 (18-35)	6.5 (4.9)	+	+	+		34 (26-42)	65 (56-80)
34	L ₁ Simul L ₂ tane L ₃ ous	153	36	33 (22-34)	8.5 (7.12)	+	+	+		23 (18-37)	40 (36-52)
29	L ₄	165	37	35 (14-44)	8.0 (6.11)	+	+	+		33 (26-40)	71 (59-87)
26	L ₅	159	32	27 (12-37)	±1.5	0	0	0	240	0	20 (15-37)

* Four to six hours postoperatively and after recovery from the anesthesia. No artificial respiration was used.

† A whining cry was noted in only 50 per cent of the observations recorded as indicating pain.

In determining the time for both the onset and the duration of pain, all five of the aforementioned criteria were taken into consideration. This accounts for the unduly prolonged intervals in the initiation of pain. However, if only the gasping, whining cry was considered as evidence of pain, its appearance and disappearance were noted within intervals of twenty seconds. Further, the cry was heard significantly earlier when tension was applied simultaneously to ligatures 1 to 3 than when applied to ligature 4 (surrounding the artery).

It must be emphasized that tension on any one or any two of the first three ligatures resulted in a direct mechanical stimulation of the coronary afferent nerve and possibly also in a chemical one, owing to

some impairment in coronary flow. Tension on ligature 4, which encircled the vessel, similarly might initiate pain, owing to both chemical and mechanical stimuli. However, with equal and simultaneous tension on ligatures 1, 2 and 3 there was only mechanical stimulation. The patency of the lumen was maintained, no ischemia resulted and hence no chemical stimulus was possible. Direct observation of the effect of tridirectional tension on the wall of the vessel by ligatures 1, 2 and 3 was made in every experiment before the pericardial cavity was closed. In no instance could any decrease in the volume of coronary blood flow be seen with the naked eye. Further proof, however, of the functional integrity of the coronary flow to the cardiac muscle, under these conditions was sought and obtained by the electrocardiographic studies, which will be presented later.

3 Blocking of stimuli by local application of alcohol was then attempted. In 2 of the dogs the procedure just cited was repeated after a few drops of 80 per cent alcohol was placed successively over the various ligatures. Application of tension on ligatures 1, 2 and 3 when alcohol was dropped over only ligature 4 gave rise to a typical pain response, however, no pain was initiated when ligature 4 or 5 was pulled on for several minutes. In like manner, no evidence of pain could be elicited by means of tension on ligatures 1, 2 and 3 after application of alcohol over these ligatures. The stimuli for cardiac pain, therefore, can be blocked by local application of alcohol whether they are initiated by a chemical or by a mechanical factor. This is in agreement with previous reports.⁹

B Determination of the Minimal Threshold of Tension—The minimal amount of tension on the ligatures in the coronary artery necessary to invoke a pain response was determined in 4 unanesthetized dogs prepared in the manner described. The ligatures were passed over a pulley and attached to varying weights exerting a vertical pull. The results obtained are given in table 2 and show that pain was initiated with a minimum tension produced by a 7 Gm weight applied to any one of the first four ligatures. With a 10 or 15 Gm weight the pain was greater and seemed to appear sooner. Five gram weights were ineffective when applied to any single ligature. In the case of ligature 5 (through the myocardium) a 25 Gm weight failed to elicit a pain response even after three minutes. When equal tension was applied simultaneously to ligatures 1, 2 and 3, marked pain was noted with the successive use of 15 and 7 Gm weights attached to each ligature, moderate pain with 5 Gm weights, mild but definite pain with 3 Gm weights and, in 1 dog only, suggestive pain with 2 Gm weights. No pain was noted in any dog when 17 Gm weights were used. One dog failed to show this pain response with a 3 Gm weight on each of the first three ligatures but responded in characteristic fashion when 5 Gm weights were employed.

It is fully appreciated that, from the few observations made, little can be concluded as to the exact amount of tension necessary to produce pain. Further, one cannot ignore the variation in response noted, which of course might easily be greater if a larger series of animals were studied. However, it nevertheless appears of remarkable interest that in some dogs, at least, mechanical tension on the wall of a coronary artery equivalent to 3 Gm on each of ligatures 1, 2 and 3 can, without impairing the coronary flow of blood, elicit the response of cardiac pain.

C Electrocadiographic Studies—The preliminary tests of applying tension simultaneously on the first three ligatures, with the animal anes-

TABLE 2—*Minimal Threshold of Tension Initiating Cardiac Pain in Four Unanesthetized Dogs*

Number of Observations	Ligature Under Tension	Weight, Gm	Pain Response*	Average Onset of Pain, Seconds
19	L ₁ or L ₂ or L ₃	5	0	
		7	+	40
		10	++	35
34	L ₁ } L ₂ } Simultaneous L ₃ }	15	+++	24
		7	+++	29
		5	++	38
		3	++	37
		2	+	42
		17	0	
29	L ₄	15	+++	32
		7	+	39
		5	0	
23	L ₅	15	0	
		25	0	

* 0 indicates no pain, +, mild pain, ++, moderate pain, +++, marked pain

thetized and the thoracic cage and pericardium open, showed that no change in color or contour of the distal region of the coronary artery and, of course, no pain response occurred. With the pericardial and thoracic cavities closed and the dog recovering from the anesthesia, several hours later, a repetition of the tests elicited in all cases the typical response of cardiac pain. It was tentatively concluded, though not fully proved, that no functional impairment in the coronary flow resulted and, therefore, that the only possible stimulus to the coronary afferent nerves was a mechanical one. During the course of the investigation Blumgart and his associates¹⁰ reported that experimental occlusion of the anterior descending branch of the left coronary artery in cats revealed within thirty seconds a characteristic elevation of the ST wave of the electrocardiogram. We had already made use of the electro-

10 Blumgart, H. L., Hoff, H. E., Landowne, M., and Schlesinger, M. J. Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries in Producing Persistent and Electrocadiographic Changes, *Am J M Sc* **194** 493-502, 1937.

cardiogram in our dogs to determine significant impairment in coronary blood flow and functioning myocardium. Proof that pain was produced without circulatory change in the muscle and hence without a chemical stimulus appears to have been established by the electrocardiographic studies now to be described.

The control and the later experimental electrocardiograms were all taken while the dogs were under pentobarbital sodium anesthesia. This precaution was necessary, since otherwise tension on the ligatures caused cardiac pain and resulted in marked movements of the body. In order to prove that these animals retained their sensitivity to pain after recovery from anesthesia, the experiments with application of tension to the various ligatures were all repeated. Typical responses of cardiac pain again were noted in every case.

Leads I to IV were taken in every case in the following order: (1) on the day preceding the experiment, to serve as a control record, (2) after surgical preparation of the animal, (3) after the application of tension (15 Gm) simultaneously on each of ligatures 1, 2 and 3 for twelve minutes, (4) after similar tension was applied for twelve minutes on ligature 5 (through the myocardium), and (5) after tension on ligature 4 (surrounding the vessel) for two to three minutes.

Electrocardiograms taken in all cases the day preceding the experiment were entirely normal. The significant changes from normal after the experimental procedures were carried out may be briefly summarized as follows:

- 1 Immediately after surgical preparation there was sinus tachycardia, and the T wave was inverted in lead III in all cases, the T wave was also inverted in leads I and II in dogs 4 and 5.

- 2 After simultaneous tension on ligatures 1, 2 and 3 or after tension on ligature 5 there was sinus tachycardia, the T wave was occasionally upright in lead II, but in most of the cases it was inverted in leads I and III. Electrocardiograms made after surgical preparation and application of tension on ligatures 1, 2 and 3 (attached to the vessel wall) or ligature 5 (inserted in the myocardium) were essentially the same and were, with the exception of changes in the T wave in leads I and II, approximately normal.

- 3 After tension on ligature 4, which surrounded the artery, for forty to seventy seconds, there was sinus tachycardia again, with occasional premature beats and elevation of the ST segment in lead IV in many beats.

- 4 After tension on ligature 4 for two or three minutes, in addition to observations noted under paragraph 3, the ST segment was elevated in leads I to III, P was upright in lead IV, Q was absent in lead IV and T was wide and notched in leads II and III, the T wave occasionally was diphasic in lead IV. The electrocardiogram made after the appli-

cation of tension on ligature 4 was typical of the electrocardiograms in cases of coronary occlusion. Figure 3 shows the electrocardiographic changes observed for a single animal (dog 4) after the various procedures just detailed.

D Pathologic Studies—In order to determine the precise location of the ligatures in the wall of the coronary artery, all the animals were studied post mortem. It was noted grossly that no ligature was torn out of place as a result of the application of tension and no hemorrhage had resulted. At the time the ligatures were implanted, no serious bleeding was observed in any of the animals. It was therefore tenta-

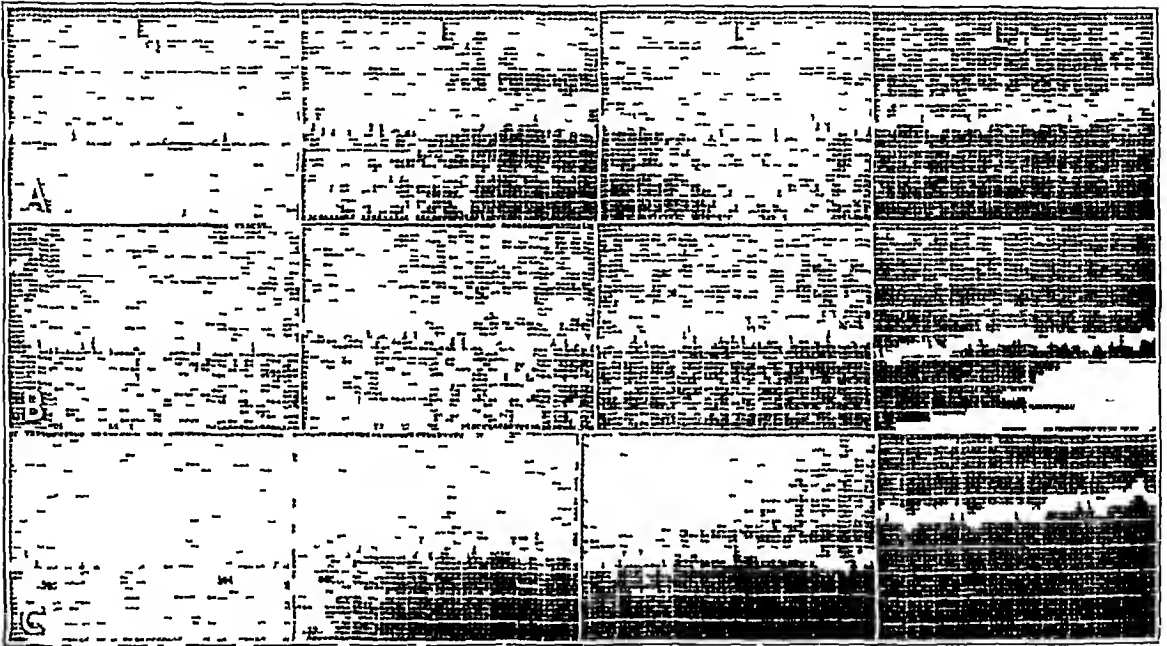


Fig 3—A series of electrocardiograms made (A) after surgical preparation of dog 4, (B) after postoperative application of tension simultaneously on coronary ligatures 1, 2 and 3 for twelve minutes and (C) after application of similar tension on ligature 4 for two and one-half minutes. Electrocardiograms A and B are essentially the same and, with the exception of changes in the T wave in leads I and II, are normal. C is typical of the electrocardiograms obtained in cases of coronary occlusion.

tively concluded that the lumens of the coronary arteries had not been pierced or torn.

Tissues from the heart were fixed in Bouin's fluid, and serial sections through the sites of the ligatures were prepared for microscopic study, hematoxylin and eosin stains being employed. Over six hundred serial cross sections were examined. In none of them was there any evidence of frank hemorrhage or of penetration or rupture of the arterial wall at any point. Surrounding the implanted silk ligatures in most cases, signs of an early acute inflammatory reaction were noted. Because of

the difficulty in sectioning tissues with embedded silk thread, it was not easy to prepare sections showing all three ligatures in position without distortion, as the thread tended to be torn out. Figure 4 *A*, however, represents a cross section of the descending branch of the left coronary

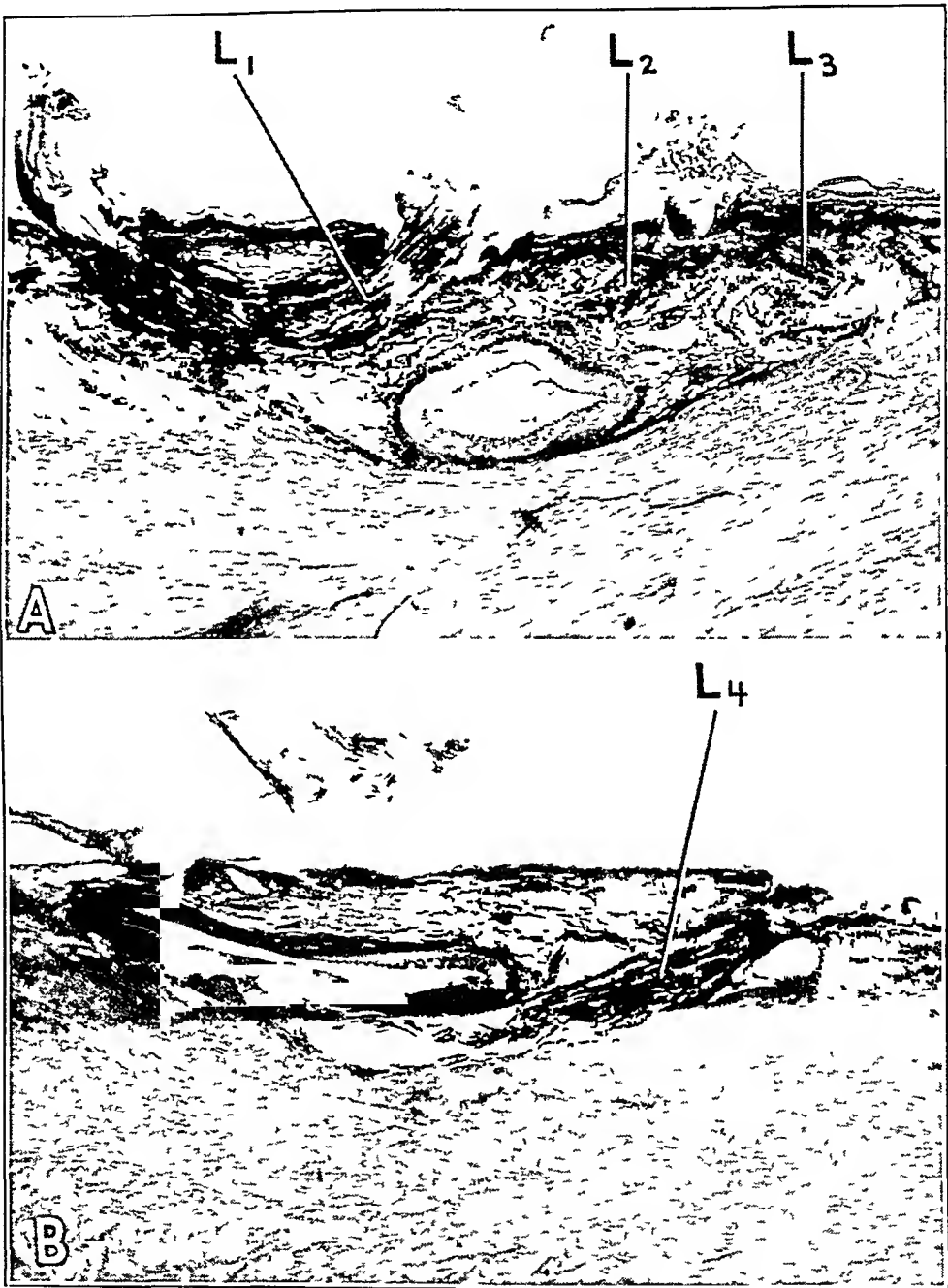


Fig 4—*A*, cross section of the descending branch of the left coronary artery of dog 4, showing the position of ligatures 1, 2 and 3 in adventitial tissue and in the same plane. *B*, another photomicrograph of the same artery, showing the position of ligature 4 underneath the vessel.

artery with ligatures 1, 2 and 3 in the adventitial tissue. In some instances ligature 1 or 3 passed through the adjacent myocardium as well as through the adventitia. The position of ligature 4, underneath

the coronary artery, can readily be seen in figure 4B. Both photomicrographs show that the continuity of the arterial wall was intact. In no instance was there evidence of injury to any part of the vessel.

COMMENT

The perception of pain is admittedly a nervous phenomenon dependent essentially on the presence and integrity of the proper receptors and their afferent pathways. With regard to cardiac pain, recent investigations have established the importance of the sympathetic afferent nerves³ in the coronary adventitia and surrounding connective tissue⁴ and their ipsilateral pathway to the spinal cord¹¹. In man and in the monkey the parietal pericardium is similarly innervated, while the myocardium and visceral pericardium are devoid of afferent nerves. In the dog both pericardial layers as well as the myocardium per se are insensitive¹². In the absence of visceral pericardial nerves, true cardiac pain in man, in the monkey and in the dog can arise only from stimulation of the afferent nerves surrounding the coronary vessels.

The natural question arises, What actually stimulates these afferent nerves? or, more properly, What factors initiate the nervous impulses? According to the prevalent theory of myocardial ischemia,⁵ impaired coronary circulation results in an abnormal accumulation of naturally occurring metabolites, one or more of which, perhaps lactic acid in particular, may irritate chemically the pain receptors. This concept is supported by many investigations¹³.

With acceptance of the statement that lactic acid, or the "P substance," is an adequate chemical stimulus, the question still remains unanswered as to how this substance, produced in the cardiac muscle, is transferred from its site of origin to the coronary afferent nerves to exert its action. Does the lactic acid, or "P substance," in the myocardium flow back upstream to reach the coronary adventitia and the branches of the nerve supply, or, more correctly, is the accumulation of lactic acid, or "P substance," in the wall of the vessel responsible for the initiation of pain? One may ask more logically, Why may not these receptors in the coronary arteries, like pain receptors elsewhere in the body, be subject to mechanical as well as chemical stimulation?

11 Moore, R. M., and Singleton, A. O., Jr. Peripheral Course of Pain Fibers Supplying Coronary Arteries and the Myocardium, *Proc. Soc. Exper. Biol. & Med.* **32**: 1492-1494, 1935.

12 Sutton and Lueth²; Katz, Mayne and Weinstein⁴; Moore and Singleton¹¹.

13 Himwich, H. E., Goldfarb, W., and Nahum, L. H. Changes of the Carbohydrate Metabolism of the Heart Following Coronary Occlusion, *Am. J. Physiol.* **109**: 403-408, 1934. Katz, L. N. The Mechanism of Pain Production in Angina Pectoris, *Am. Heart J.* **10**: 322-327, 1935. Wiggers, C. J. The Physiology of Cardiac Pain, in Lévy, R. L. Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Co., 1936, chap. 6, p. 177. Sutton and Lueth².

The modified technic of Sutton² has afforded an opportunity to investigate the probable importance of the mechanical factor in initiating cardiac pain. It is believed that adequate care has been exercised to eliminate the chemical stimulus. Our experiments showed that cardiac pain was experienced by unanesthetized dogs by means of simultaneous tridirectional tension on the wall of the coronary artery. That there was no material impairment of the coronary blood flow under these conditions was evidenced by the absence of electrocardiographic changes. We feel convinced that the mechanical or tension factor in the absence of a chemical one can be an effective stimulus for producing cardiac pain. Shambaugh¹⁴ has shown that the pain response can be elicited in dogs if the aortic blood pressure is suddenly increased in the presence of subminimal constriction of the coronary vessels. The epinephrine used to produce the rise in aortic blood pressure also dilates the coronary vessels. This sudden dilatation may, in itself, mechanically stimulate the onset of pain. When elasticity is reduced, as in a sclerosed vessel, tension may be minimized, and painless coronary occlusion may be expected.⁷

Our experiments do not offer any direct evidence to disprove the possibility of the generally accepted theory that ischemia is the cause of cardiac (coronary) pain, but they do prove that pain may be produced mechanically in the absence of any chemical stimulus. The proponents of the theory of ischemia, on the other hand, have not yet demonstrated experimentally that pain can be produced by a chemical stimulus alone in the absence of any mechanical factor.

The onset of cardiac pain caused by simultaneous tension on ligatures 1, 2 and 3 (lying in the adventitia) is much quicker than that caused by tension on ligature 4, which surrounds the coronary artery. The intensity of the pain is greater also in the first instance even though the pull exerted is approximately the same. These facts may possibly be explained by supposing that a more effective stimulus is evoked by ligatures placed in the nerve-bearing adventitia than can be aroused by a ligature encircling the entire vessel. The cessation of pain is more prompt on release of the three ligatures inserted in the wall of the vessel than it is when the artery is both occluded and pulled by ligature 4.

Although the minimal threshold of tension necessary to initiate cardiac pain was determined, it is at best only approximate and holds true only for the dog. Further, the method used to determine the degree of tension necessary is subject to criticism in that the variation in the pressure in the coronary artery, the more natural mechanical stimulus, has not been estimated. This fact is thoroughly appreciated and will be investigated in subsequent studies.

14 Shambaugh, P. Circulatory Changes in Angina Pectoris. An Experimental Study, *Arch Int Med* 56:59-76 (July) 1935.

SUMMARY

An attempt has been made to determine the role of the mechanical factor in the initiation of cardiac pain in dogs recovering from anesthesia. It has been found that a typical pain response can be elicited when tridirectional tension in one plane is applied to a coronary vessel in such a manner as to cause no change in blood flow. With this procedure the chemical factors caused by impaired coronary blood flow are completely eliminated, as shown by the absence of changes in the electrocardiogram. The minimal threshold of tension on ligatures in the coronary vessel was 3 Gm in the series of dogs used. Local application of alcohol can block stimuli initiating cardiac pain, whether mechanical or chemical in origin. It is concluded that tension alone on the coronary arteries in dogs may serve as an adequate stimulus for the initiation of cardiac pain.

Dr Arthur W Wright, of the Department of Pathology, cooperated by preparing the histologic material used in this study. Miss M L Smith and Miss A P Schafer were of technical assistance in the preparation of the illustrations.

COCCIDIOIDES INFECTION (COCCIDIOIDOMYCOSIS)

II THE PRIMARY TYPE OF INFECTION

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Ever since coccidioidal infection has been known to be due to a fungus,¹ it has been recognized that there are two distinct cycles of development of the infecting organism the form which occurs when the organism has infected animal tissues, and the one which occurs when the organism grows on culture medium and, presumably, in nature. The first of these cycles was that observed when infected human beings came under clinical observation. The parasitic organism was seen as a double-contoured spherule, averaging about 30 microns in diameter, which reproduced by endosporulation, the endospores being released into the tissues by rupture of the wall of the mother spherule. The spherules so closely resembled *Coccidia* that it was at first believed that they belonged to the protozoan group, and they were called *Coccidioides*, like *Coccidia*, hence the name. The second cycle occurs when the organism grows outside the body, the vegetative stage, and here it appears as a white moldlike fungus which reproduces by the formation of chlamydo-spores. The chlamydo-spores are numerous and light and are easily transported in the air, particularly when associated with dust.

Since the earliest studies of the disease coccidioidal granuloma, there has been great interest in how the infection is acquired by man and, much more recently, by certain domestic animals, viz, cattle and sheep. As early as 1905 Ophüls² wrote concerning a case which occurred in California in 1900, "These observations prove the occurrence of primary

The study of coccidioidomycosis is being aided by the Rosenberg Foundation, San Francisco

From the Department of Public Health and Preventive Medicine, Stanford University School of Medicine, San Francisco, and the Kern County Department of Public Health, Bakersfield, Calif

1 Ophüls, W, and Moffitt, H C. A New Pathogenic Mould (Formerly Described as a Protozoan *Coccidioides Immitis* Pyogenes), Philadelphia M J 5 1571, 1900

2 Ophüls, W. Further Observations on a Pathogenic Mould Formerly Described as a Protozoon (*Coccidioides Immitis*, *Coccidioides* Pyogenes), J Exper Med 6 443, 1900-1905

pulmonary infection in this disease, very probably due to inhalation of the parasitic organism which causes it" In 1929 Ophuls still held the opinion that inhalation of chlamydospores is an important factor, for when discussing the papers by Cummins, Smith and Halliday and by Pulford and Larson, he said ³

For the mode of infection, all evidence so far gathered seems to point to respiratory involvement with a primary localization of the virus in the lung. In almost all cases that have come to autopsy, it is possible to find an old primary focus in the lungs, and the pulmonary lesions are often of great clinical and pathologic importance. The infecting agent is evidently the spore which develops on the aerial hyphae of the mycelium of the fungus. It is probably the spores of the fungous growth that becomes mixed with dust and are then inhaled into the lungs. The finding of the disease in animals such as cattle and sheep does not seem to me to suggest that the infection is from animals to human beings. It is much more likely that the animals contract the disease much in the same way as human beings do in the infected region.

The majority of workers, however, have apparently disregarded the fact that in the vegetative stage of growth the fungus *Coccidioides* reproduction is accomplished by means of chlamydospores and have had their attention focused on the endospores, which are seen exclusively when the organism has become involved in its parasitic phase. Since prolonged observation has failed to show any person to person or animal to person infection, there has been nothing to show how this disease may be transmitted, if one fails to remember that the chlamydospores of the vegetative stage may be responsible for the primary infection. Various possible methods of transmission, even including transmission by insects,⁴ as in tularemia or Rocky Mountain spotted fever, have been suggested, but none has been proved to be adequate.

Unquestionable proof that inhalation of chlamydospores of the fungus *Coccidioides* will cause infection of human beings was given by the case of a young man who became infected in the laboratory of the Department of Public Health and Preventive Medicine at Stanford University Medical School. His case was mentioned in a previous report in the ARCHIVES OF INTERNAL MEDICINE ⁵ and more fully discussed later in *California and Western Medicine* ⁶. In the latter report 4 other cases were cited in which the patients had acquired their illness

3 Ophuls, W., in discussion on Cummins, W. T., Smith, J. K., and Halliday, C. H. Coccidioidal Granuloma, J. A. M. A. **93** 1046 (Oct 5) 1929. Pulford, D. S., and Larson, E. E. Coccidioidal Granuloma, *ibid* **93** 1049 (Oct 5) 1929.

4 Jacobson, H. P. Fungus Diseases, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 213.

5 Dickson, E. C. Coccidioides Infection. Part I, Arch. Int. Med. **59** 1029 (June) 1937.

6 Dickson, E. C. "Valley Fever" of the San Joaquin Valley and Fungus Coccidioides, California & West. Med. **47** 151, 1937.

in the San Joaquin Valley and were typical cases of the "valley fever" or "desert fever" of that district. This disease has been recognized frequently in the San Joaquin Valley, but so far as we can learn had not hitherto been described in the medical literature. The first time it was mentioned in an official publication was in the annual report to the county supervisors by the Kern County Department of Public Health for 1935-1936, where it was described as San Joaquin fever.

The frequency of the disease is indicated by replies to a questionnaire which was mailed on May 15, 1937, to physicians who were practicing in eight counties of the San Joaquin Valley. They were asked how many cases of San Joaquin fever or erythema nodosum had been recorded since Jan. 1, 1936. Of 127 physicians who replied, 52 reported that they had recorded no cases during that time, but 75 reported that they had

Cases of Valley Fever Recorded by Seventy-Five Physicians in the San Joaquin Valley, Calif., from Jan. 1, 1936, to May 15, 1937

	Fresno	Kern	Kings	Madera	Merced	San Joaquin	Stanislaus	Tulare	Totals
Number of doctors reporting cases	19	10	7	6	4	12	7	10	75
Number of cases reported	69	117	24	31	11	29	18	55	354
Males	27	48	6	9	4	15	5	25	139
Females	42	69	18	22	7	14	13	30	215
Fever	68	117	17	30	11	27	15	52	337
Cough and sputum	19	48	6	22	1	4	9	15	124
Recovery without complication	65	115	20	31	11	15	17	51	325
Progressed to typical coccidioidal granuloma		1							1

recorded 354 cases up to May 1937. The accompanying table shows in what counties these 75 physicians were located and that the occurrence of cases was recognized in all parts of the San Joaquin Valley, although more frequently in the southern counties. For instance, 263 of the 354 cases were reported from Fresno County and the counties south of Fresno.

It was found that valley fever occurs at all seasons of the year. Of the cases reported in the answers to this questionnaire, 32 per cent had their onset in the spring, 23 per cent in the summer, 25 per cent in the autumn and 20 per cent in the winter. Both sexes were affected, 138 cases (39 per cent) were in males and 216 (61 per cent) were in females. Persons of all ages were included. 3 per cent were children of preschool age, 18 per cent were children of school age, 51 per cent were young adults and 28 per cent were persons over 40. It is particularly interesting that all 354 patients but 1 recovered without complications after an illness of a few weeks. In 1 patient coccidioidal meningitis developed and was fatal.

The onset of the acute illness is often spoken of at first as a bad cold or "flu." Usually the patient complains of feeling ill, with headache and often with general body aches and pains. Some complain especially of aches and pains about the chest, as in pleurisy, and some of indefinite gastrointestinal disturbance. Frequently there is a history of mild sore throat, which is sometimes attributed to tonsillitis. Occasionally there is some conjunctivitis, with hyperemia of the scleras but with nothing suggestive of phlyctenules. Fever may begin at the time of onset of symptoms or four or five days later, after distress in the upper respiratory tract has attracted attention. Not infrequently the temperature is not higher than 100 to 101 F, but sometimes, usually later, when signs of bronchopneumonia appear, it may be 104 or even 105 F. Once in a while a patient has an early chill, and some complain of sweating, but chills and sweats are not constant.

There is usually bronchitis, sometimes with unproductive cough, but varying amounts of sputum are common. It appears that cough and the production of sputum occur relatively early and often cease after a few days. At times the sputum is produced in considerable amount and may be streaked with blood. Often the patient improves after a few days' illness and feels that he is getting better, but in from eight to fifteen days after the onset, erythematous nodules develop on the skin, these are described popularly as bumps. The lesions are typically those of erythema nodosum in most cases, but sometimes have the appearance of erythema multiforme.

The erythema nodosum usually appears primarily on the shins, where the nodules are most numerous. Not infrequently they may occur on the thighs, sometimes on the buttocks or on the arms and occasionally in the scalp or on the upper portion of the thorax, producing a collar-like arrangement around the root of the neck. The lesions do not fluctuate or suppurate but may be fiery red and so tender or painful that the weight of the bedclothes may be disagreeable. At other times they are merely hypersensitive. Within from forty-eight to seventy-two hours they begin to turn purplish and fade, and in four or five days they have usually disappeared except for a brownish pigmentation, which may persist for weeks after the tenderness and swelling have disappeared. Occasionally, but rarely, there may be a successive crop of erythema nodosum after an interval of three or four weeks.

The temperature usually subsides gradually after the "bumps" disappear (fig 1), and usually there are no recurrences. The leukocyte count usually ranges from normal to about 15,000, but the differential count often shows eosinophilia. The highest eosinophil count which we have seen was 8 per cent on the day the "bumps" first appeared, which

increased to 13 per cent five or six days later and then dropped to 2 per cent. In 1 case in which there were two crops of erythema nodosum about four weeks apart, there were 10,800 leukocytes, with 7 per cent eosinophils, with the first attack and 5,500 leukocytes, with 5 per cent eosinophils, at the time of the second attack. In the interval between the two outcroppings the eosinophil count was not higher than 2 per cent. In another case, one in which there was no erythema nodosum, the patient suffered pains in the wrists and ankles at the time

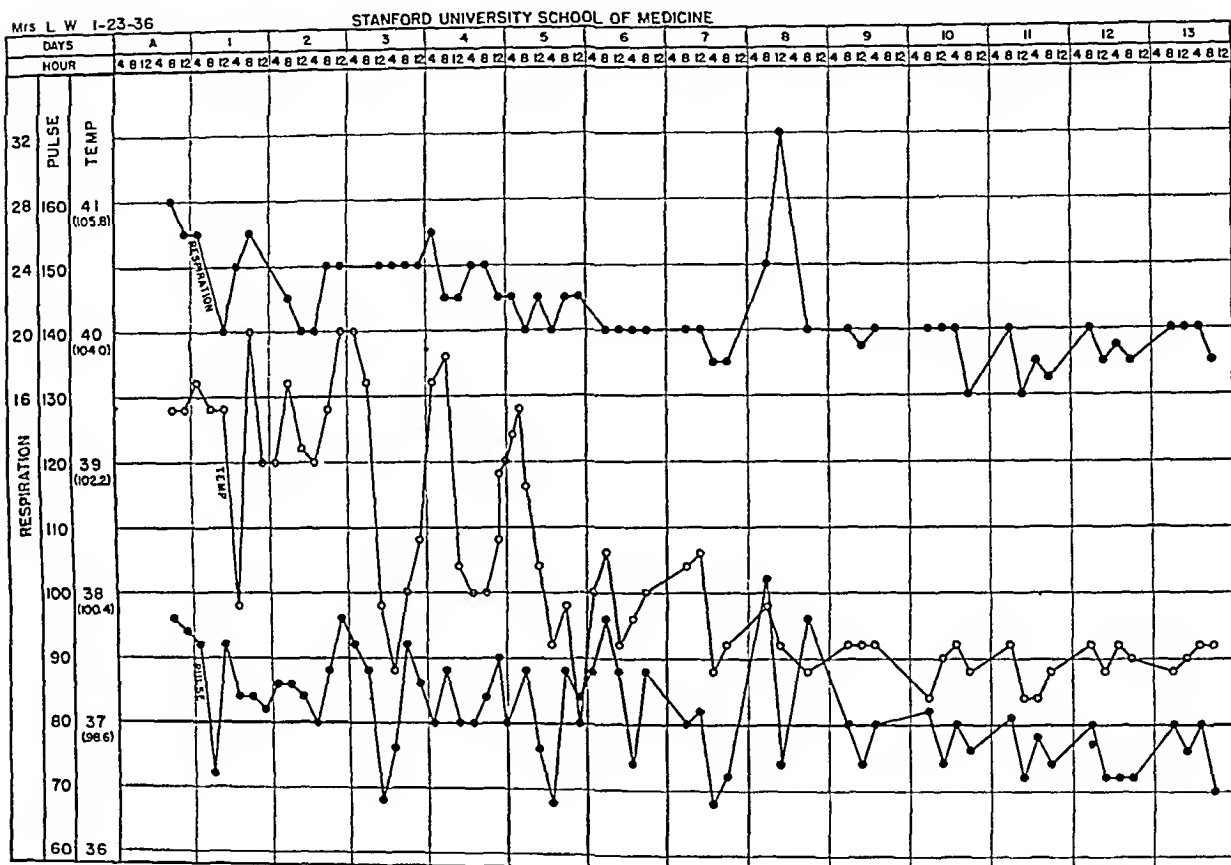


Fig 1—Temperature chart. The patient had valley fever and entered Stanford University Hospital at the time erythema nodosum appeared.

the erythema nodosum might have been expected, and during that period there were 8 per cent eosinophils.

A diagnosis of valley fever is seldom if ever made before the erythema nodosum is present, in fact, the presence of erythema nodosum is one of the manifestations on which the diagnosis depends. It is the tenderness or pain in the erythematous lesions, the so-called bumps, which brings many of the patients under medical attention. It is said that a large percentage of patients never seek medical attention at all, particularly if the erythematous lesions are not painful; and it is known that some patients infected with *Coccidioides* have an

illness which is diagnosed as "flu" or have more or less severe pneumonia without the occurrence of erythema nodosum. Consequently, it is often said that there is no sputum when the patient comes under medical observation, although there may be a history of some cough with sputum at the beginning of the acute attack. In reply to the questionnaire in which 354 cases of valley fever were reported, of only 174 was it stated that there were cough and sputum at the time of erythema nodosum, but at the Stanford University laboratory forty-three specimens of sputum from patients with valley fever have been received for examination, of which thirty-six contained *Coccidioides*. Most of the sputums containing *Coccidioides* were collected between from six to twenty days after the date given as that of the onset of acute illness, but there was 1 case in which the sputum still showed the fungus after two months. Specimens from patients in hospitals in San Francisco showed the fungus when collected from seventeen to thirty days after the onset of illness. It should be remembered that for children who are too small to raise sputum, gastric lavage is necessary, as in early tuberculosis. In 1 such case the washings obtained by gastric lavage contained mucopurulent material in which were sporulating and nonsporulating spherules of *Coccidioides*. Pure culture of the fungus was obtained from the mucopurulent material, and guinea pig inoculation proved that it was a virulent *Coccidioides*. It was also found that the coccidioidal spherules were soon digested out by the acid gastric secretion.

The laboratory diagnosis of *Coccidioides* from a study of the sputum is not difficult if one but remembers to look for the spherules. Characteristic spherules may be seen in fresh cover slip preparations in many instances. All that is necessary is to study the fresh unstained specimen under a microscope, with the illumination cut down, as for examination of urinary sediment for casts. Plain spherules or spherules with endospores may be seen, the double-contoured capsules being distinct with a low degree of illumination. It should be remembered that the spherules average about 30 microns in diameter. Stained smears are less satisfactory than fresh cover slip preparations, because the spherules are likely to be distorted during the process of drying and fixing. The fungus grows readily on ordinary culture mediums, but for diagnostic purposes Sabouraud medium is preferable. Growth of the fungus usually appears in from forty-eight to seventy-two hours, but a culture should not be called sterile until at least a full week of incubation has elapsed. The colony appears as a white fungous growth, which gradually enlarges until it may be 1 inch (2.5 cm) or more in diameter when on an agar plate. It consists of white, finely branched mycelium

For differential diagnosis of the fungus and to establish its virulence, it is necessary to inject the fungus into a guinea pig. If male animals are selected and intraperitoneal injections are given, it will be found that the testicles enlarge, as in glanders, within two or three weeks. When the animal is killed, in about one month or six weeks, there is extensive involvement in the organs of the peritoneal cavity, often in the lungs, in the omentum and in the regional lymph glands, as well as in the testicles. Pus from the lesions shows many sporulating and nonsporulating spherules of *Coccidioides*. By intratesticular injection



Fig 2—Roentgenogram of a patient with valley fever in the Kern County Hospital, Bakersfield, Calif. *Coccidioides* was recovered from the sputum.

the time necessary for identification of the spherules in pus from the testicles may be reduced to from ten to fourteen days.

If roentgen examination of the chest is made at the time the erythema nodosum appears, opacities in the pulmonary shadows are seen which have often been described as indicating tuberculosis (fig 2). For instance, concerning the first patient who was observed, a young man who was infected in a laboratory, Dr W E Chamberlain, then at Stanford University Medical School, wrote in his report of Sept 19, 1929:

Roentgenographically there seems to be massive involvement of the upper lobe of the right lung with tuberculosis, lobar pneumonia is, of course, a possibility

from the roentgenographic standpoint, but my impression is that the clinical picture rules out pneumonia and makes tuberculosis the much more likely explanation

On October 17, approximately one month later, Dr Chamberlain reported

The abnormal densities in the left lung have entirely disappeared The abnormal densities in the upper lobe of the right lung are considerably more than half gone, there remains just a trace of the former mottling and consolidation in the caudal portion of the upper lobe

In another case, that of a 24 year old man who was admitted to Kern County Hospital, in Bakersfield, Calif, the following roentgenographic report was made "A differential diagnosis between a bilateral exudative type of tuberculosis and bilateral bronchopneumonia with interlobar empyema of the right side must be made" A subsequent roentgenogram of the chest, four and a half months after his discharge from the hospital, showed both lungs clear Typical *Coccidioides*, proved virulent by guinea pig inoculation, was recovered from the sputum in both of these cases

Similar reports have frequently been made by many roentgenologists who have examined patients with so-called valley fever The typical picture includes evidence of enlargement of the hilar glands, branching shadows from the hilar region of the lungs and more or less scattered areas of shadows indicating involvement of the parenchyma of the lung, in either the upper or the lower lobes Signs of pleurisy, pleurisy with effusion or interlobar empyema may be seen at times

It is characteristic in the great majority of cases of acute coccidioidomycosis that when roentgen examination of the chest is made from one to several months after the acute illness, it is found that the earlier pulmonary lesions, which appeared so similar to those of tuberculosis, have entirely disappeared and the lungs are described as clear (figs 3 and 4)

Use of coccidioidin is particularly valuable in the diagnosis of valley fever Coccidioidin is a specific antigen used in making cutaneous tests It was first recognized by Davis,⁷ in 1924, and later studied by Hirsch and Benson,⁸ da Fonseca and de Arêa Laño⁹ and Jacobson¹⁰

7 Davis, D J Coccidioidal Granuloma, with Certain Serologic and Experimental Observations, *Arch Dermat & Syph* 9 577 (May) 1924

8 Hirsch, E F, and Benson, H Specific Skin and Testis Reactions with Culture Filtrates of *Coccidioides Immittis*, *J Infect Dis* 40 629, 1927

9 da Fonseca, O, and de Arêa Laño, A E Réaction cutanée spécifique avec le filtrat de cultures de *Coccidioides immittis*, *Compt rend Soc de biol* 97 1796, 1927

10 Jacobson, H P Coccidioidal Granuloma Specific Allergic Cutaneous Reaction, Experimental and Clinical Investigations, *Arch Dermat & Syph* 18 562 (Oct) 1928



Fig 3—Acute infection with *Coccidioides* (valley fever) The sputum showed *Coccidioides* A, roentgenogram taken at the Kern County Hospital, Bakersfield, Calif, on July 29, 1936 B, roentgenogram taken on Dec 14, 1936

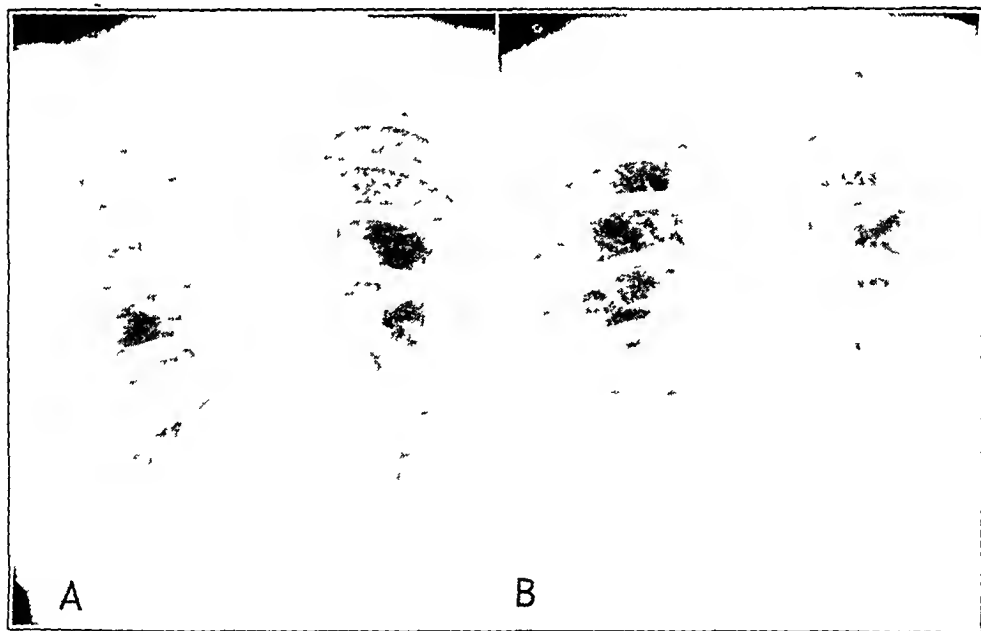


Fig 4—Acute infection with *Coccidioides* (valley fever) The sputum showed *Coccidioides* A, roentgenogram taken at the Kern County Hospital, Bakersfield, Calif, on March 9, 1937 B, roentgenogram taken on Oct 14, 1937

It was described by Jacobson⁴ as the filtrate of a broth culture of *Coccidioides* which has been incubated from ten to thirty days and then passed through a Berkefeld filter. Kessel¹¹ modified this by grinding a portion of the mycelium of the culture and adding it to the broth before filtration. The method of use is the same as the Mantoux method of testing with tuberculin. Jacobson reported that for general diagnostic work for infection with *Coccidioides*, 0.1 cc of the filtrate is injected intracutaneously and if a positive reaction is obtained the characteristic local area of erythema is produced, which reaches its maximum intensity, often with some vesiculation, in about forty-eight hours. The lesion produced begins to fade in a few days and usually has disappeared in from eight to fourteen days, but local pigmentation of the skin may persist for a variable time thereafter.

The length of time after infection that sensitization of the patient may occur is not known, but in guinea pigs and rabbits which have been infected by inhalation of chlamydospores, the coccidioidin tests first give a positive reaction six or seven days after the inoculation. The length of time the sensitization lasts is also unknown, but persons who have been examined ten years after having valley fever have shown a strongly positive reaction to coccidioidin, although they had shown no indication of coccidioidal lesions since the occurrence of valley fever and were apparently entirely free from them at the time of examination.

Patients who are suffering from valley fever, the initial acute infection of the respiratory tract with the chlamydospores of *Coccidioides*, react acutely to the coccidioidin test. It has been found that with some lots of coccidioidin the intracutaneous injection of 0.1 cc may produce a severe reaction or even local necrosis of the skin in some cases. It has therefore been found desirable to use diluted coccidioidin, up to 1:1,000 dilution of some specimens, for the initial test. With a specimen of coccidioidin which we are using at present, it has been found that for the initial test it is preferable to use 0.1 cc of 1:1,000 dilution, followed if necessary by 0.1 cc of 1:100 or of 1:10 dilution. It should be emphasized that it is necessary to use a syringe and needle which have not been used for tuberculin, as otherwise the reaction may be confusing if the patient shows a positive reaction to the tuberculin test.

It is unfortunate that up to the present no method for standardization of coccidioidin has been perfected, and it is impossible to predict its potency except by clinical trial. The active antigenic substance has not been identified. The closest laboratory method of standardization is to study the comparative reaction in infected guinea pigs or rabbits,

11 Kessel, J. F. Personal communication to the authors

but there is so little known about variations in the intensity of the infection and the possibility of varying degrees of sensitivity to different intensities of the infection that at present the differences in the reaction of laboratory animals is not satisfactory for standardization of material to be used on human beings

The incidence of valley or desert fever, that is, the incidence of cases in which the initial symptoms resembled influenza, or "flu," bronchitis and sometimes pleurisy or bronchopneumonia, followed by an outbreak of erythema nodosum, is high in the San Joaquin Valley. The demonstration that the great majority of specimens of sputum from patients with valley fever have been shown by culture and guinea pig inoculation to contain virulent *Coccidioides* indicates that the majority if not all cases of valley fever are caused by infection with *Coccidioides*. And the fact that the great majority of patients with valley fever survive without apparent complications proves that infection with *Coccidioides* is not, in all stages of the disease, the highly fatal disease which it has been believed to be. From 1894 to July 1937, 495 cases of coccidioidal granuloma were reported in California, with 249 deaths, therefore, the mortality from coccidioidal granuloma in California has been practically 50 per cent. However, the great majority of patients with valley fever survive, among the 354 patients in the series mentioned, only 1 showed coccidioidal granuloma and died. Hence, the mortality rate of patients who acquire infection with *Coccidioides* is extremely low. The actual mortality rate cannot be estimated until there are accurate data concerning the actual incidence of cases of the preliminary acute infection.

But it has been found in a number of cases of acute infection with *Coccidioides* that erythema nodosum has not developed, therefore, these cases have not been included in the group of cases of valley or desert fever, usually or often the condition is classified as "flu." In a number of such cases *Coccidioides* has been recovered from the sputum, but the percentage of such cases is not known. However, in the cases in which coccidioidal granuloma has developed some have been noted in which there was no history of erythema nodosum, as well as cases in which there was a history of such an illness. The incidence of valley fever, therefore, does not indicate the total incidence of acute infection with *Coccidioides*.

REPORTS OF CASES

The following brief abstracts of case histories indicate the various types which have been discussed. The first group of 5 were of the type in which a diagnosis of valley fever was made, that is, cases in which erythema nodosum was present.

CASE 1¹²—A white farm laborer aged 23 had been exposed to dust in Kern County while harrowing. He had lived in Kern County for three months. On Dec 6, 1936, a severe cold developed, with pains in the chest. During the following two weeks he felt ill and had a small amount of tenacious sputum. On December 18 a rash developed which simulated rose spots on the arms and lower portion of the abdomen, but this was entirely cleared within three days. On December 24 he had erythema nodosum on the legs, from the knees down. The lesions were tender, reddened "bumps," which he described as being "sore as a boil."

Roentgen examination of the chest showed a feathery infiltration of the parenchyma of the lungs and considerable hilar adenopathy. The sputum contained typical spherules of *Coccidioides*. The leukocyte count was 17,850, with 2 per cent eosinophils. The coccidioidin test gave a strongly positive reaction, a well marked bleb and edema developed, with an erythematous area measuring 25 by 35 mm in diameter.

After a troublesome illness the patient became afebrile and apparently recovered completely. On Sept 3, 1937, a roentgenogram showed that both pulmonary fields were entirely clear.

CASE 2¹²—A white woman aged 41 had been picking cotton in Kern County, where she had lived for seven months. She complained that the cotton was dusty. On Dec 24, 1936, she complained of fever, pains in the chest, cough and soreness throughout both sides of the chest. She entered the Kern County Hospital on January 4, where a diagnosis of infection of the upper respiratory tract was made. She left the hospital on January 12, against her physician's advice, because she was feeling so much better. On January 14 reddened, tender, swollen "bumps" developed on the anterior and posterior surfaces of the legs and on the thighs. The roentgenogram of the chest taken on January 25 showed increased density in the right hilar region, with small projections extending into the pulmonary fields. The coccidioidin test showed a central bleb, measuring 20 by 25 mm, surrounded by a hyperemic area, measuring 80 by 100 mm.

The leukocyte count was 6,850, with 78 per cent polymorphonuclear neutrophils. Culture of the sputum showed growth of a white mold, and on guinea pig inoculation infection with *Coccidioides* was produced. The patient recovered.

CASE 3—A white boy aged 3½ years was brought to the Stanford University Hospital from Tulare County on April 13, 1937. His mother said he had had fever for two weeks and painful red nodules on the shins for two days. On March 27 he had become irritable and complained of sore throat. His temperature was 100 F, and it was considered that he had a cold. For a time there was constipation, with cramps in the bowels. The fever continued, and a few days after the onset the temperature ranged between 103 and 104 F. At this time there was a so-called heat rash on the trunk and neck, which lasted for one or two days. Two days before his admission to the hospital red, painful nodules appeared on the shins, lower portion of the thighs and buttocks which reached their maximum intensity within forty-eight hours and then began to fade. The child had become apathetic, had slept poorly and had had "night cries" for about four days before entry. A diagnosis of valley fever had been made by the local physician in Tulare County.

12 This patient was treated in the Kern County Hospital, and the case was included in the annual report of the Kern County Department of Public Health, 1936-1937.

On physical examination nothing unusual was detected except the lesions on the lower extremities, the buttocks, the extensor surface of the right forearm and just above the left elbow. The nodules were warm, red and purplish red, indurated and tender but not painful, they were discrete or confluent. On the shins they were up to 3 cm in diameter, but elsewhere they were not larger than 1.5 cm.

A tuberculin test gave a negative reaction, but the coccidioidin test gave an extremely positive reaction, so marked that for a time local necrosis of the skin was feared. The blood count showed 8,200 leukocytes, with 53 per cent polymorphonuclears and 3 per cent eosinophils. The sedimentation test was rapid—31 mm in sixty minutes.

Because there was no expectorated sputum, gastric lavage was done. The stomach washing contained mucopurulent material in which typical spherules of *Coccidioides* were seen. Culture and guinea pig inoculation proved that the diagnosis was infection with *Coccidioides* (fig 5).

A roentgen examination of the chest was made on April 14, and it was reported as follows: The pulmonary roots were heavy, particularly on the left side. There was also some parenchymal infiltration on the left side at the level of the seventh and eighth ribs posteriorly. The pleura between the upper and the lower lobe was thick. In conclusion it was reported that the appearance was compatible with tuberculosis (fig 6).

The child made an uninterrupted recovery and appeared to be well. On June 26, 1937, a second roentgenogram of the chest was reported as showing that the density in the lower lobe of the left lung had cleared remarkably, leaving only the faintest perceptible granularity in that region.

CASE 4—A white man aged 26, a medical student, was planning work with *Coccidioides* in a laboratory of Stanford University Medical School. On the first day, Aug 29, 1929, that he worked with the fungus he inadvertently opened a Petri dish containing a plate culture which was several months old. He noticed a fine brownish dust rise from the culture. Undoubtedly they were chlamydo-spores. No other opportunity for infection was known.

On September 6, eight days later, he noticed pains in the chest, resembling the pain of pleurisy, which rapidly increased in severity. In the evening a physician could find no signs of involvement in the chest but strapped it to give relief. The temperature at the time was 99 F. For the next nine days he was far from well and tired easily. His cough became more severe, and he was obliged to spend part of his time in bed. In the morning there was much purulent sputum, which was sometimes streaked with blood. He had nearly constant headache, backache and aching in the legs. He felt that he had a fever but did not use a thermometer. On September 19 he found that he had lost 15 pounds (6.8 Kg) in two weeks.

The patient was then confined to bed, and it was found that the temperature ranged between 99 and 100 F. A blood count showed 10,800 leukocytes, with 57 per cent polymorphonuclear neutrophils and 7 per cent eosinophils. The eosinophil count decreased in a few days to 2 per cent.

On September 25 a red, painful nodule appeared on one shin, and the next day there were several similar nodules on both shins. They were red, hot and tender and measured about 1.5 cm in diameter. They began to subside by September 30 and on October 3 were practically gone. On November 14 there was a second crop of similar lesions on the shins, which reached their maximum size in two or three days and then disappeared. The eosinophil count at that time was 5 per cent of 5,500 leukocytes.



Fig 5—Petri dish culture of mucopurulent material recovered by gastric lavage (see fig 6)

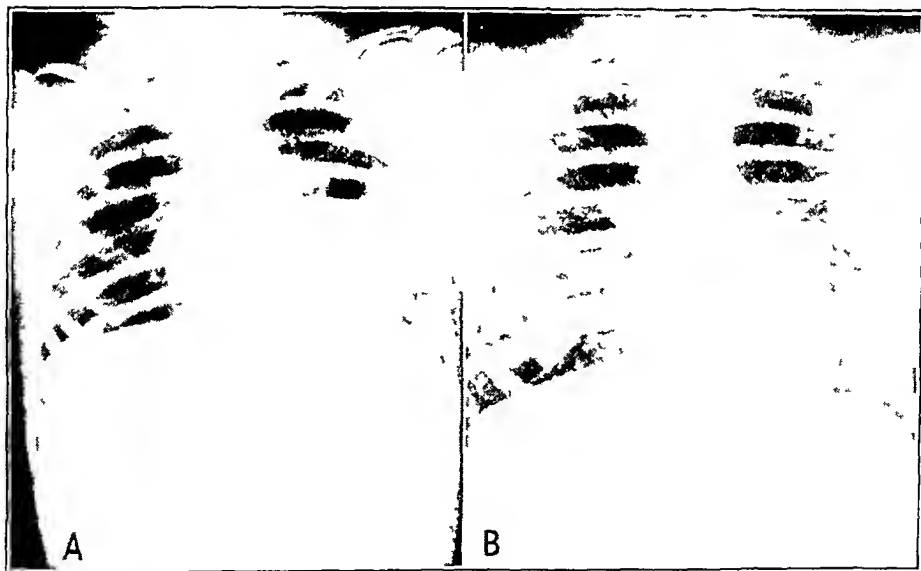


Fig 6—Acute infection with *Coccidioides* (valley fever) The sputum (see fig 5) showed *Coccidioides* A, roentgenogram taken on April 14, 1937 B, roentgenogram taken on June 23, 1937

On November 25 his physician noted that he was progressively better. There was no cough or any other pulmonary symptoms.

The first sputum culture was made on September 24 and the last on September 27. The production of sputum ceased on that date, and no further specimens could be obtained. Examination of the sputum on September 26 showed no acid-fast bacilli. Cover slip preparations contained a moderate number of coccidioidal spherules; the majority were nonsporulating, and a few had endospores. Culture showed the characteristic fungous growth, and guinea pig inoculation resulted in typical lesions due to *Coccidioides*.

The roentgen examinations of the chest made on September 19 and October 17 have already been reported on. Subsequent examinations have been made frequently, and it has always been reported that the lungs were clear. The patient has been apparently well since the summer of 1930.

Comment—The next case proves that typical acute valley fever may progress to coccidioidal granuloma and cause death.

CASE 5¹²—A 50 year old white housewife had lived in Kern County for two months. She and her family were obliged to live in an auto camp beside a highway which was being graded and therefore were exposed to heavy clouds of dust. On Nov 6, 1936, she had a severe cold, pleurisy and cough, with expectoration of thick, glairy, mucopurulent sputum. The thoracic symptoms improved in about three weeks, and erythema nodosum then developed, with characteristic "bumps" on the legs, thighs, forearms and hands. In December she entered Kern County Hospital, complaining of symptoms of meningitis. Repeated spinal punctures and finally trephine of the skull were performed to relieve the headaches and vomiting. The patient grew steadily weaker and died on May 13, 1937. At autopsy basilar coccidioidal meningitis was evident, culture and guinea pig inoculation of purulent exudate from the base of the brain proved that the infection was due to *Coccidioides*.

The white blood cell count was 12,800, with 61 per cent polymorphonuclear neutrophils. A roentgenogram of the chest taken on January 22 showed increased density of the parenchyma of the lower lobe of the left lung.

Comment—It has already been stated that in all cases of acute primary infection with the chlamydospores of *Coccidioides*, erythema nodosum does not develop and therefore not all cases are classified as cases of valley fever, some being classified as cases of "flu" or bronchopneumonia. The following cases were of the latter type.

CASE 6—A white man aged 26, a field geologist, was working on a "dusty job" in Kern County in December 1929. On December 28 he did not feel well and two days later had nausea, vomiting and diarrhea for one day, followed by constipation. On Jan 1, 1930, he had stabbing pains in the upper left portion of the chest, but this soon subsided. The temperature was 100.5 F. He continued to feel ill and was able to work only part time. On January 9 and 10 he had aching pains in the ankles and wrists and began to cough and raise sputum. He was admitted to the hospital on January 14, complaining of pain, fever, malaise, cough and expectoration. The detailed hospital record is not available, but a diagnosis of bronchopneumonia was made. The temperature was 103.2 F on the day of entry but was down to normal in four days. It did not rise again thereafter.

On January 14 a roentgenogram of the chest was reported as showing rather marked enlargement of the hilar glands, with slight, coarse mottling throughout the upper half of the left lung. It was concluded that the patient had tuberculosis. On January 28 another roentgenogram of the chest was reported as showing slightly less prominent markings than on the previous examination. On March 24 it was reported that the lungs were clear.

Examination of the sputum on January 27 was reported as showing no acid-fast bacilli or spherules of *Oidia*. On Sabouraud medium there was a fungous growth which was said to resemble that of *Coccidioides*. On February 21 it was reported that a guinea pig which was given an injection of the culture of the sputum showed generalized infection with coccidioidal granuloma.

It was a feature of this case that there was no erythema nodosum, but on January 7 and January 13 it was noted that there were 4 per cent and 6 per cent eosinophils, respectively, just before and after the patient complained of pains in the ankles and wrists. The patient made an uninterrupted recovery from the acute illness.

CASE 7¹³—A Negro boy aged 15 was first seen in Fresno, Calif., on Sept. 14, 1936. About the middle of August 1936 he became ill, with chills, afternoon fever, night sweats and cough with sputum. He lost about 22 pounds (10 Kg.) in three weeks. Tuberculosis was suspected because fluoroscopic examination showed infiltration of the left lung, with the densest part near the hilus. Serial roentgenograms made in the Alameda County Hospital, to which he was referred, showed rapid clearing of the infiltration in the left lung. He remained in the hospital for two months. The sputum and stomach washings did not show tubercle bacilli, and guinea pig inoculation did not cause tuberculosis.

On December 4 the boy was seen in the clinic and said he had been feeling well and was gaining weight. Roentgen examination showed that the lung had cleared except for heavy peribronchial markings toward the base of the left lung.

On January 8 he still felt well but showed a hard, diffuse swelling on the left forearm just below the elbow. A roentgenogram showed no lesion of the bone, but by February 10 a small sinus had opened from this area. On February 19 a similar swelling was present on the left thigh just above the knee. This was fluctuant at the center, and fluid was removed by aspiration. This was proved by culture and guinea pig inoculation to contain *Coccidioides*.

The roentgenograms of the chest, when viewed from the standpoint of acute infection with *Coccidioides*, seemed to be identical with those of patients with acute valley fever (fig. 7). The maximum lesion was at or near the hilus and was associated with parenchymatous shadows, which cleared rapidly. It seems probable, therefore, that the acute onset was due to primary infection with *Coccidioides*, without erythema nodosum, which was followed by lesions of coccidioidal granuloma in the extremities.

CASE 8¹⁴—A white man aged 41 was first seen by his physician on July 26, 1936, for acute infection of the upper respiratory tract. The physician made a diagnosis of pneumonia and sent the patient to a hospital. Bacteriologic exami-

13 Reported to us by Dr. G. E. Koerber, of Oakland, Calif.

14 This case was reported by Dr. De W. Higgs, of Chula Vista, Calif. Autopsy was performed by Dr. H. A. Ball, of the San Diego General Hospital, San Diego, Calif.

nation of the sputum showed growth of a white fungus. The patient made a fair recovery and was sent home. There was no history of erythema nodosum.

About six weeks later the patient had an acute attack, accompanied by numbness of the arms and legs and marked dizziness. For a few days he continued to work but became progressively worse and was again sent to the hospital. After a severe illness with marked mental derangement, he died in February 1937. Autopsy was performed on February 26. The anatomic diagnosis was coccidioidal granuloma with chronic basilar meningitis. The only coccidioidal lesion reported, other than those in the meninges, was a small fibrocaseous nodule, measuring slightly more than 1 cm. in diameter, in the upper lobe of the left lung. Culture could not be made because the body had been embalmed, but smears showed numerous pus cells and spherules of *Coccidioides* in various stages of development.

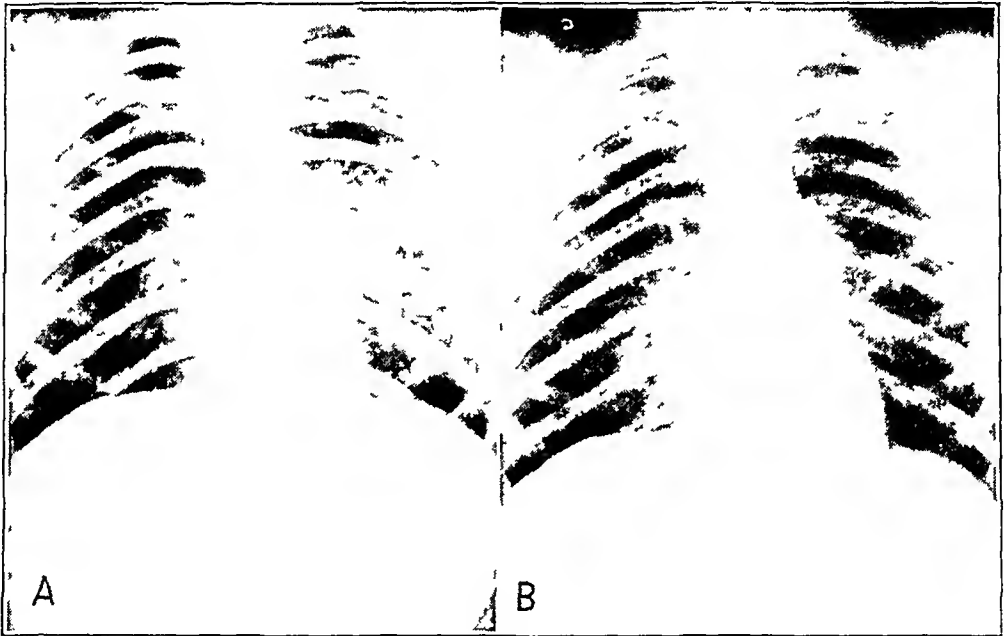


Fig 7—Acute infection with *Coccidioides* (valley fever) followed by coccidioidal granuloma. A, roentgenogram taken at the Alameda County Hospital, Oakland, Calif., on Sept 17, 1936. B, roentgenogram taken on April 19, 1937.

COMMENT

It follows that acute primary infection with the chlamydospores of *Coccidioides* is of frequent occurrence in the San Joaquin Valley and usually causes a mild disease from which the great majority of victims recover without apparent complications. In a few cases coccidioidal granuloma subsequently develops when the causative organisms become disseminated by the blood stream. No attempt has been made in this report to discuss the pathology of primary infection due to *Coccidioides*, but it may be said that in guinea pigs and rabbits which are forced to inhale the chlamydospores of the vegetative phase of the growth of the fungus, interstitial pneumonia is produced which tends to clear promptly

In the acute disease there is no immediate formation of tubercles, but the process is apparently limited to changes which follow the absorption of the chlamydospores by the lymphatic system. Roentgenograms of the chest of the infected animals show the same hilar and parenchymatous shadows in the lungs, which clear promptly, as those in human beings. After such a process there is marked enlargement of the peribronchial lymph nodes which drain the pulmonary field.

The reaction to inhaled chlamydospores, therefore, is a temporary irritation of the lymphatic system which does not cause immediate destruction of tissue and severe tissue damage or the production of granulomatous changes. When the chlamydospores are injected subcutaneously or into the blood stream, on the other hand, the foci of infection which are induced are typically granulomatous, and there are many spherules. Reproduction of the fungus in the parasitic phase is by endosporulation, and if the spores gain access to the blood stream they may be widely disseminated.

It is obvious that the well established name coccidioidal granuloma is not applicable to primary infection due to inhalation of the chlamydospores of *Coccidioides*, because the immediate reaction to such a type of infection is not to produce granulomas. It is desirable, therefore, to have some name which is applicable to all types of infection with *coccidioides*, whether primary or progressive (secondary).

In a previous report⁶ the same coccidioidomycosis was suggested. This corresponds in form to such accepted terms as actinomycosis and blastomycosis, which indicate infection with the fungi *Actinomyces* and *Blastomyces*, respectively. Individual cases can be classified as due to primary coccidioidomycosis and progressive (secondary) or granulomatous coccidioidomycosis with further classification indicating the site of the granulomatous lesions if desired.

Such a nomenclature is somewhat cumbersome, it is true, but its use indicates recognition that there are different manifestations of infection with *Coccidioides* and that coccidioidal granuloma is not a disease entity but a late progressive or secondary phase of an infectious disease which is caused by the fungus *Coccidioides*.

SUMMARY

It has been shown that infection with the fungus *Coccidioides* may cause disease of a primary or secondary progressive type.

The primary form of the disease is due to inhalation of the chlamydospores formed in the vegetative phase of the growth of *Coccidioides*.

Infection with *Coccidioides* is common in the San Joaquin Valley in California, it is usually mild, and the great majority of patients recover without complications.

The condition is often diagnosed as a bad cold or 'flu' in the beginning, but when erythema nodosum occurs in its course it is popularly known in the San Joaquin Valley as desert or valley fever.

In a few cases the condition subsequently progresses to the highly fatal disease known as coccidioidal granuloma.

The name coccidioidomycosis has been suggested to include all types of infection with the fungus *Coccidioides*.

PULSATING ANGIOMA (GENERALIZED TELANGIECTASIA) OF THE SKIN ASSOCIATED WITH HEPATIC DISEASE

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The association of two uncommon and apparently unrelated conditions in the same patient is unusual. When this association occurs more frequently than can be explained by mere coincidence it must have some significance. Such an association was first drawn to attention when Osler¹ observed that "angiomata have a curious relationship with affections of the liver." It seems that this association is more frequent than a review of the literature indicates, and it is my purpose to draw further attention to it, review the pertinent facts and present 6 cases recently observed at the Mayo Clinic.

CHARACTERISTICS OF CUTANEOUS ANGIOMA

Though the cutaneous vascular lesions vary considerably in appearance, depending on their size, they all exhibit two essential characteristics: (1) a central angiomatous portion and (2) radiating telangiectatic vessels. The central portion varies from a bright red, punctate vascular point to a deep red, smooth, compressible elevation the size of a pea. Parkes Weber² was the first to note pulsation in this central eminence. In smaller lesions the radiating telangiectatic vessels may be limited to two or three fine, threadlike strands extending from 0.5 to 1 cm from the central point. The medium-sized lesions exhibit a border, 1 to 2 cm in width, made up of numerous radiating stellate telangiectatic vessels, producing a spider or medusa-like effect. The entire lesion may be suffused a dusky red from dilatation of deep lying vessels.

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1 Osler, W. On a Family Form of Recurring Epistaxis, Associated with Multiple Telangiectases of the Skin and Mucous Membranes, *Bull Johns Hopkins Hosp* **12** 333-337 (Nov) 1901

2 Weber, F. P. Haemorrhagic Telangiectasia of the Osler Type—"Telangiectatic Dysplasia." An Isolated Case, with Discussion of Multiple Pulsating Stellate Telangiectases and Other Striking Haemangiectatic Conditions, *Brit J Dermat* **48** 182-193 (April) 1936

In the largest lesions a few of the radiating vessels may assume the appearance of small, tortuous cyanotic varicosities. The smaller lesions are indistinguishable from naevus araneus, or spider nevus, seen commonly on the cheeks of children.

In most instances the lesions are limited to the skin of the head and neck, of the upper part of the chest and shoulders and of the fingers, dorsa of the hands and forearms. Occasionally they may be generalized, but in such cases most of them are in the sites mentioned. A prominent feature is the occurrence of lesions on the nasal and buccal mucosa. Slight trauma to any of the lesions, the nasal ones in particular, may give rise to alarming hemorrhage. The familial tendency which is prominent in some cases has caused the condition to become known as familial or hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber syndrome).

HEPATIC DISEASE

The associated hepatic disease is usually chronic, and the findings of cirrhosis with splenomegaly preponderate. Arsenic, alcohol and syphilis are the common etiologic agents. Low grade hepatitis, splenic anemia and a malignant growth of the metastatic type have been observed. The concomitant changes in the constituents of the blood resulting from the hepatic disturbance are seen, and ascites, icterus and splenomegaly are frequent. The familial tendency observed in cases of cutaneous angioma is not so obvious in cases in which there is associated hepatic disease, van Bogaert,³ however, has presented 2 cases of familial hepatic cirrhosis with angioma.

The relation of the time of the onset of the cutaneous lesions to that of the onset of the hepatic disease is of interest. In most cases the angiomas appear first, and frequently they antedate the hepatic disturbance by fifteen to twenty years. Usually the patient states that a few small, isolated lesions on the face or epistaxis (indicative of lesions of the nasal mucosa) was noted a number of years prior to the onset of symptoms and signs of hepatic disease. With the onset of the hepatic disease the cutaneous lesions often increase rapidly in size and number. It is not unusual to observe partial regression of the angiomas with improvement in the hepatic condition. Although difficult to prove, it seems likely, since the hepatic disease is chronic, that the damage to this organ may antedate the clinical appearance of symptoms by a long period, it is, in fact, possible that the damage might even date back to the time of the onset of the cutaneous angiomas.

3 van Bogaert, L, and Scherer, J H. Hémangiomatose familiale de Rendu-Osler et cirrhose hépatique, contribution à l'étude des cirrhoses familiales, *Ann de med* 38 290-300 (Oct) 1935

Data on Cases of Cutaneous Angioma (Generalized Telangiectasia) with Hepatic Disease Reported in the Literature

Case	Author	Age, Yr, and Sex	Cutaneous Angiomas			Hepatic Disease			Pathologic Observations
			Age at Onset, Yr	Site	Pathologic Observations	Family History	Type	Age at Onset, Yr	
1	Osler ¹	55 M	Child hood	Face, ears, tongue, eyes and nasal mucosa	Large dilated veins	+	Carcinoma, metastatic	55	Splenomegaly 0 0
2	Galloway, J Proc Roy Soc Med (Clin Sect) 4 42, 1911	35 M	34	Face, neck, shoulders and extremities		0	Hepatomegaly, syphilitic	30	0 0
3	Fricks, W J Cutan Dis 30 334, 1912	50 M	35	Generalized	Dilated capillaries	0	Carcinoma, metastatic	49	0 0
4	Roles, F O, cited by Fitz Hugh 9 677, 1930	65 F		Face, lips, tongue and hands		0	Cirrhosis		0 +
5	Coursemann, H Klin Wchnschr 54 677, 1930	54 M		Face, lips and palate		+	Splenohepatomegaly		0 +
6	Fitz-Hugh, T, Jr Am J M Sc 181 261, 1931, case 1	65 F	25	Face, lips and nasal mucosa		+	Splenohepatomegaly	58	+
7	Fitz Hugh, case 2	48 F	Early adult hood	Face, lips and nasal mucosa		+	Splenohepatomegaly	46	0 +
8	Fitz Hugh, case 3	40 F	21	Face, lips, tongue and fingers		+	Splenohepatomegaly	38	0 +
9	Fitz Hugh, case 4	58 F	Adolescence	Face, lips, nasal mucosa and fingers		+	Splenohepatomegaly	37	0 +
10	van Bogaert and Scherer, ³ case 1	73 F	40	Face and hands		+	Familial cirrhosis		0 +
11	van Bogaert and Scherer, ³ case 2	46 M	45	Face and fingers		+	Familial cirrhosis	15	+
12	Coffin, J, and Bastenle, P Bruxelles méd 14 577, 1934	50 F		Face, tongue, lips and nasal mucosa		+	Hepatomegaly		Hemorrhages, fatty degeneration
13	Milbradt, W Dermat Wchnschr 99 973, 1934	47 F	41	Face, tongue, lips and nasal mucosa		+	Cirrhosis	41	+
14	Weber ²	41 M	41	Face, neck, chest and left arm	Dilated capillaries with small round cell infiltration	0	Cirrhosis (syphilitic?)	41	
15	Eller, J J Arch Dermat & Syph 36 892, 1937	45 F	41	Cheeks, trunk, legs, arm and oral and nasal mucosa		0	Hepatomegaly (alcoholic cirrhosis?)	44	0 0

REVIEW OF THE LITERATURE

Fifteen cases of cutaneous telangiectasia with associated hepatic disease have been recorded. A summary of these cases is presented in the accompanying table. There were 6 men and 9 women, ranging in age from 35 to 73 years, most of them being in the fifth or sixth decade of life. The cutaneous vascular lesions of the "spider" or a naevus araneus type were observed on the face, neck, nasal mucosa, tongue, lips and hands. In most instances they had appeared during adulthood, and they usually antedated, but often increased rapidly in extent and number with the onset of, the symptoms of the hepatic disorder. In 10 of the cases there was associated familial hemorrhagic telangiectasis. Hepatic cirrhosis was present in 5 cases, metastatic carcinoma of the liver in 2 and hepatosplenomegaly of an undiagnosed type in 6. Jaundice was noted in 2 cases, splenomegaly in 8, syphilis in 1 and pulmonary tuberculosis in 1. Alcohol seemed to be a factor in at least 3 cases. A rare finding in van Bogaert's 2 cases was the presence of both familial cirrhosis and familial telangiectasia.

MATERIAL IN PRESENT STUDY

Six cases of cutaneous angioma of the stellate type associated with hepatic disease have been encountered recently at the Mayo Clinic. The angiomas presented the characteristics previously described. It was noted that when pulsation could not be felt in small lesions, it could be demonstrated by gentle pressure with a diascope. In only 1 instance was there a suggestive familial tendency. The tendency for the cutaneous lesions to antedate the clinical appearance of hepatic disease was apparent. In contrast to the age range of the patients reported on in the literature, 3 of the patients in the present series were adolescent. The hepatic disease was predominantly of the cirrhotic type, in 2 cases this was proved at necropsy. In 2 cases syphilis was present, which together with the fact that arsenic was probably used therapeutically may have been an etiologic factor.

REPORT OF CASES

CASE 1—A college student aged 18 years was seen at the clinic in February 1937. He had been jaundiced for approximately two and a half months. There were no other complaints of consequence. The patient was well nourished and muscular but was slightly pale and moderately jaundiced. Numerous pulsating spider angiomas were observed over the face and over the dorsum of each hand. There was no familial history of such cutaneous lesions. The liver was large and firm, the spleen was also readily palpable. Examination of stained smears of the blood showed moderate hypochromic macrocytic anemia. The value for serum bilirubin varied from 3.2 to 4.5 mg per hundred cubic centimeters. The value for blood cholesterol was slightly reduced, and the value for plasma protein was lowered (5.8 Gm per hundred cubic centimeters, with an albumin-globulin ratio

of 1 2) A bromsulphalein test of hepatic function showed grade 3 retention of the dye. The sedimentation rate was considerably increased (117 mm in one hour). A diagnosis of subacute hepatitis with jaundice and pulsating cutaneous angioma was made.

CASE 2—A girl aged thirteen years was brought to the clinic in September 1936 with the complaint of jaundice and of lesions of the skin. The family history was significant in one respect, in that a sister had a few angiomas on her face. During the first four months of the patient's life she had been definitely jaundiced. This had eventually cleared up, however, and she was well until 1932. At that time angiomas were first noticed on her face, and two years later some appeared on her fingers. Early in 1936 a large number of angiomas appeared on her arms, neck and lips. In April 1936 jaundice again made its appearance, and a month later epistaxis occurred on several occasions. At the time of the patient's last examination she was in excellent general condition except for the fact that she showed the large number of angiomas already referred to and definite jaundice, the liver was large and firm and the spleen extended 2 cm below the costal margin. Macrocytic anemia was noted. A bromsulphalein test of hepatic function showed grade 3 retention of the dye. The value for serum bilirubin averaged 8 mg per hundred cubic centimeters. The fragility of the erythrocytes was normal. A flow of bile was obtained on duodenal drainage.

The patient's general condition remained satisfactory until Sept 17, 1937, when abdominal pain, chills and fever suddenly developed, her temperature rose to 105 F and she lapsed into coma. Treatment with continuous venoclysis of dextrose was given, and consciousness was regained on the sixth day. Three days later abdominal distention and vomiting developed, followed immediately by gross bleeding from the intestinal tract. The patient died on September 27. Necropsy revealed chronic atrophy of the liver, the organ showing signs of previous extensive necrosis and some areas of nodular regeneration. Free bleeding had occurred into the stomach and intestine. Multiple hemorrhagic ulcers of the ascending colon and edema of the mucosa were also observed, their exact significance could not be determined. The spleen was hypertrophic, weighing 230 Gm.

CASE 3—An unmarried housekeeper aged 35 years registered at the clinic in April 1932. She complained principally of anemia and weakness, splenomegaly had been noted some time previously and she came seeking advice concerning the advisability of splenectomy. On physical examination there were no striking findings except moderate pallor and splenomegaly. Examination of the blood revealed hypochromic anemia, with rather striking leukopenia and a reduction in the number of blood platelets. The value for serum bilirubin was normal, the van den Bergh reaction was indirect and the bromsulphalein test of hepatic function showed grade 3 retention of the dye. On April 2 the spleen, weighing 650 Gm, was removed by Dr Pemberton. The liver was described as decreased in size and definitely nodular. A specimen for biopsy showed changes rather typical of those of atrophic cirrhosis. There was no ascites, and no extensive collateral circulation had developed. A diagnosis of Banti's disease with portal cirrhosis was made.

The patient has been seen at the clinic at intervals since that time, and the only development of significance has been the appearance of a large number of spider angiomas over the face, trunk and arms. Repeated tests of hepatic function have shown continued improvement.

CASE 4—A laundryman aged 52 years has been seen at the clinic at various times since 1918. At the time of his first visit he had definite clinical and serologic evidence of *tabes dorsalis* and was given adequate treatment with arsphenamine and heavy metals. In 1918 jaundice developed during a course of treatment, this persisted for several weeks but gradually cleared. On examination two years later the liver was found to be enlarged and firm. In 1932 ascites developed, and a Talma-Morison omentopexy was performed elsewhere. The liver at that time was described as showing definite evidence of cirrhosis. In April 1937, the patient was again seen at the clinic and was markedly jaundiced. There were multiple large pulsating angiomas of the stellate type scattered over the face, particularly around the eyes (fig 1), and over the upper part of the trunk. The liver and spleen were both enlarged and readily palpable. Serologic tests for syphilis gave positive reactions, the formed elements of the blood were entirely normal except for a slight increase in the reticulated cells (41 per cent) and moderate macrocytosis. Roentgenologic examination for esophageal varices

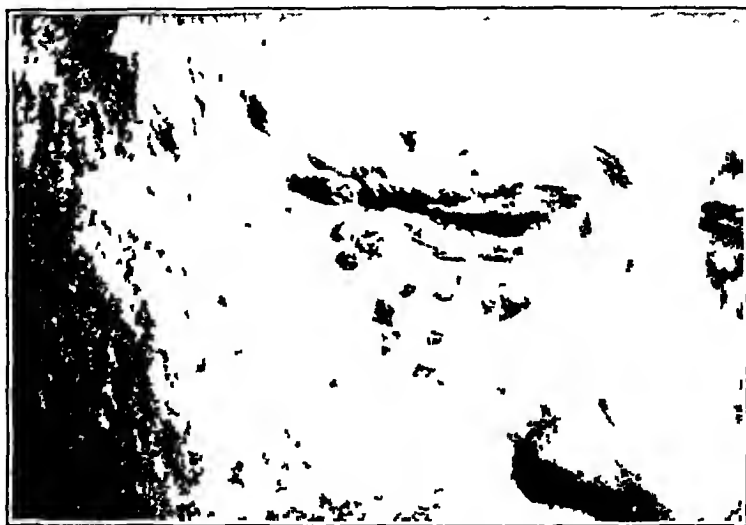


Fig 1 (case 4)—Pulsating angiomas involving the eyelids

gave negative results. A bromsulphalein test of hepatic function showed grade 2 retention of the dye. The blood gave a direct van den Bergh reaction, and the serum bilirubin reading was 52 mg per hundred cubic centimeters. The value for serum protein was normal, but the value for cholesterol was considerably reduced (106 mg per hundred cubic centimeters). A diagnosis of atrophic cirrhosis on a syphilitic basis was made. Word was received that the patient died in May 1937. The postmortem observations were not available.

CASE 5—A cafe operator aged 41 years registered in May 1937 for consideration of his complaint of swelling of the abdomen and legs of three weeks' duration. He had been seen at the clinic in 1925 with a latent syphilitic infection of four years' duration and had been given adequate treatment with the arsenicals and bismuth. A long history of alcoholic excess was noted. Examination revealed scattered stellate angiomas on the face (fig 2) and trunk of approximately fifteen years' duration. The liver was tremendously enlarged and firm, and the spleen was just palpable (fig 3). There was considerable ascites, and a collateral circulation was visible. Serologic tests for syphilis gave positive reactions, and the bromsulphalein test of hepatic function showed grade 3 retention of the dye. The value for blood cholesterol was normal. Examination of the formed elements of the blood revealed slight macrocytosis.



Fig 2 (case 5) —A large pulsating angioma is seen on the right cheek, and numerous small lesions are scattered on the lips, neck and adjacent upper portion of the chest



Fig 3 (case 5) —Ascites and enlargement of the liver and spleen (outlined)

On histologic examination the pulsating lesion on the cheek was found to be an elevated cavernous hemangioma extending from the pars subpapillaris down deep into the cutis. A stroma of loose, young connective tissue surrounded the vascular spaces. On the periphery of the central angiomatous portion of the lesions there was telangiectatic dilatation of the vessels of the subpapillaris

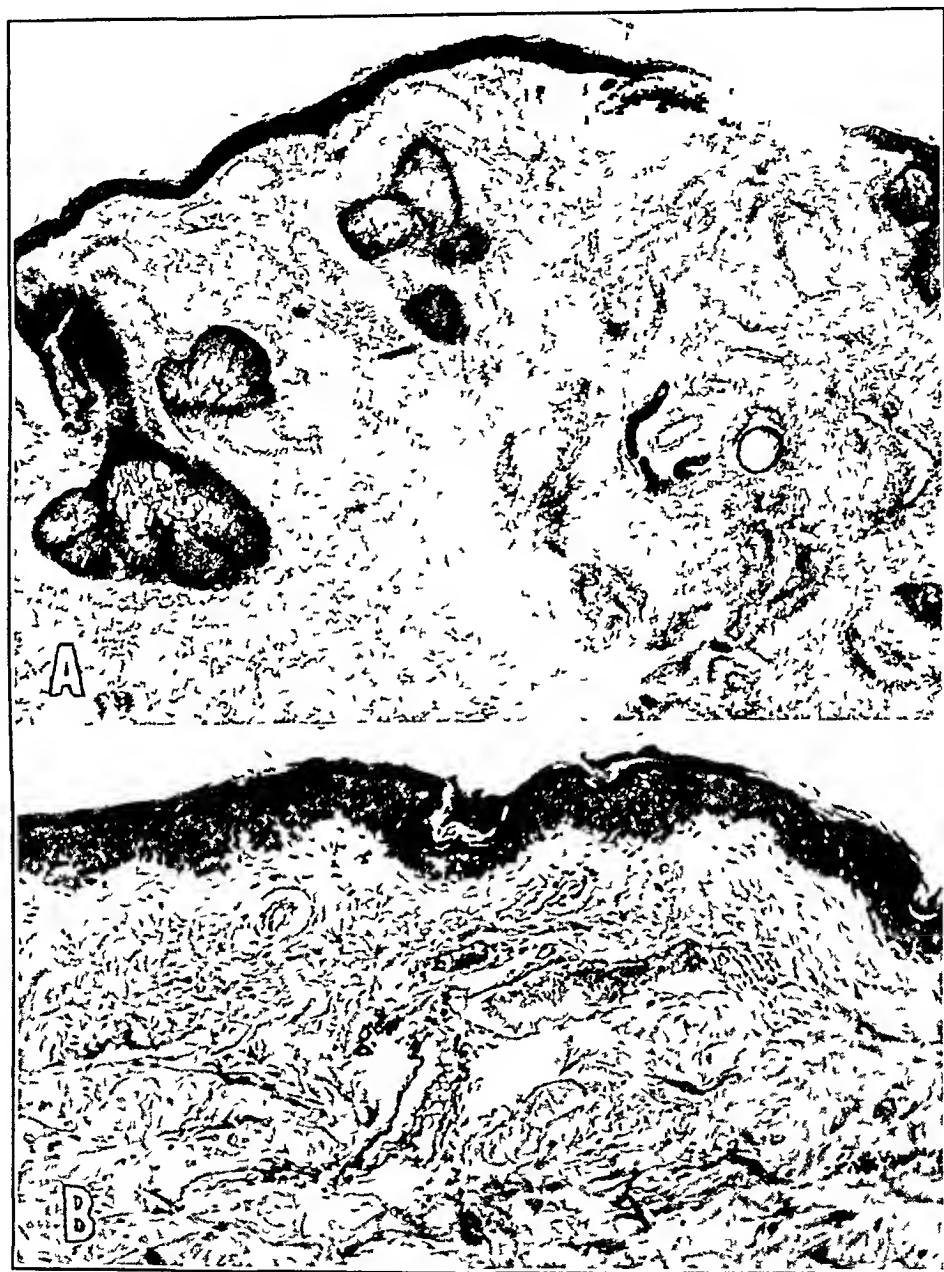


Fig 4 (case 5) —Sections of the large angioma from the right cheek, showing (A) the central angiomatous portion and (B) the peripheral telangiectatic dilatation of a blood vessel in the upper portion of the cutis

Figure 4 shows the central angiomatous element and the peripheral telangiectatic portion of the lesion. A diagnosis of cirrhosis of the liver and pulsating angioma was made, and it was considered that both syphilis and alcohol were factors in the causation of the hepatic disease.

CASE 6—A girl aged 12 years was admitted to the clinic in September 1937 with the complaint of recurrent nosebleeds and jaundice of one year's duration. Elsewhere the spleen and liver had been found to be enlarged. On examination at the clinic the patient was found to be moderately jaundiced, the liver and spleen were enlarged and there were many stellate pulsating angiomas scattered on the face, neck, arms, hands and right leg. These had been present since the age of 4 years. Laboratory examination revealed values for serum bilirubin which varied from 5.2 to 6.3 mg per hundred cubic centimeters, a direct van den Bergh reaction being recorded. The values for plasma protein were normal. A galactose tolerance test gave a positive result, raising the suspicion of recent hepatic injury. The cholesterol reading was 116 mg per hundred cubic centimeters of blood. The formed elements of the blood were not unusual except for a reticulocyte count of 10.6 per cent. During the period of observation the patient had an afternoon temperature of from 99 to 102 F. On October 12 Dr. Walters performed an exploratory operation. The liver was enlarged, and the bile passages showed no signs of past or present obstruction. Cholecystectomy was performed.

One week later the patient became drowsy and semistuporous, blood oozed from around the drainage tube. Death occurred on the eleventh postoperative day, the typical manifestations of hepatic insufficiency being present. Necropsy revealed chronic atrophy of the liver, with marked fibrosis and nodular hyperplasia, the spleen was hypertrophied, weighing 257 Gm. Multiple subpleural and epicardial hemorrhages were also seen, but there was no gross bleeding into the digestive tract, such as occurred in case 1.

COMMENT

The nature of the association of cutaneous angioma and disease of the liver gives rise to much speculation. The established facts concerning it are few. The terms telangiectasis and angioma, applied by different authors to the same cutaneous lesion, imply the concept of an acquired dilatation of existing blood vessels, on the one hand, and the concept of a neoplastic growth, on the other. As a result of the histopathologic examination of a lesion in case 5, it seems likely that both concepts are true, that the lesions are in effect both angiomatous and telangiectatic and that the former condition is primary and the latter secondary.

The feature of pulsation observed by Paikes Weber is an important characteristic, and it suggests a possible relation of the lesion to the glomus bodies described by Masson⁴. Further work is being carried out relative to this point. It is not difficult to conceive how a lesion causing marked dilatation of this arteriovenous anastomosis might result in a cutaneous lesion with the characteristics of pulsation and radiating telangiectasia. In addition, glomus bodies are most frequent on the hands, and it is here that the angiomas are numerous.

⁴ Masson, M. P. Les glomus cutanes de l'homme, *Bull Soc franç de dermat et syph* 42 1174-1245 (July 7) 1935.

That the lesions under consideration are identical with those of hereditary hemorrhagic telangiectasia is apparent from a review of the literature and the reason why a hereditary tendency is present in some cases and is not apparent in others is best explained on the basis that this familial characteristic is transmitted as a dominant in some persons and as a recessive in others. The characteristic appears to be dominant in hereditary hemorrhagic telangiectasia, whereas it is probably recessive when there is no definite hereditary or familial tendency.

Why a certain percentage of persons born with the inherent characteristic either dominant or recessive, of being likely to have cutaneous pulsating angiomas should also be born with a liver in which cirrhosis is likely to develop cannot be explained. Possibly these two inherent characteristics are closely related. That there is some factor directly affecting the two conditions is demonstrated by the definite increase in the number of the angiomas with the onset and progression of clinical evidence of hepatic damage and by the fact that occasionally improvement in the hepatic disease has been reported to have coincided with regression of the angiomas.

It is interesting to note, as recorded by Weber,⁵ that hepatic cirrhosis may be familial (dominant characteristic). He explained the vascular lesions on the basis of "a congenital-developmental dysplasia of the small blood-vessels, potentially present at birth, though often not manifesting itself by obvious changes till after puberty." He continued as follows: "What is the relationship of the hepatic cirrhosis, when present? Is it the result of an associated developmental dysbiotrophy of the liver—i. e., a congenital tissue or organ inferiority?"

Hanes,⁶ and later Gjessing,⁷ drew attention to the absence of muscular and elastic tissue elements in the vessel walls in cases of hereditary telangiectasia. Memmesheimer⁸ noted that the connective tissue in the vicinity of the dilated vessels consisted of a proliferation of young, not well differentiated connective tissue elements. These workers claimed that this inherent weakness in the walls of the vessels and in the supporting connective tissue is a predisposing factor in the development of the vascular lesions. What is the exciting factor which seems so

⁵ Weber, F. P. Inborn and Familial Tendency to the Development of Hepatic Cirrhosis, *Lancet* 1:305-307 (Feb. 8) 1936.

⁶ Hanes, F. M. Multiple Hereditary Telangiectases Causing Hemorrhage (Hereditary Hemorrhagic Telangiectasia), *Bull. Johns Hopkins Hosp.* 20: 63-73 (March) 1909.

⁷ Gjessing, E. Telangiectasia hereditaria haemorrhagica (Osler), *Dermat. Ztschr.* 23:193-211, 1916.

⁸ Memmesheimer, A. M. Zur Pathogenese der sogenannten essentiellen Telangiectasien, *Dermat. Ztschr.* 53: 399-413 (April) 1928.

closely related to the liver? The absence of evidence of a toxic or of an infective factor is seen from microscopic examination of the cutaneous lesion, which is, instead, of a neoplastic nature.

From this rather abstruse consideration of a probably not infrequent association come a few practical considerations. Since as a rule the cutaneous manifestations of this syndrome appear before the hepatic manifestations, whenever the former are encountered they should prompt a thorough examination of the liver and its functions, further a person who exhibits such lesions should be looked on as a possible candidate for hepatic disease, and the use of hepatotoxic drugs such as arsenic and alcohol should be interdicted. A corollary to the foregoing is that in chronic hepatic disease pulsating cutaneous angioma will probably be encountered more frequently if one is watching for it. It appears that the association is not uncommon.

SUMMARY AND CONCLUSIONS

The association of cutaneous pulsating angioma (generalized telangiectasia) and hepatic disease is not uncommon. This association probably depends on two inherent developmental characteristics which are closely related.

The cutaneous lesions are primarily angiomatous in nature and have a border of radiating telangiectatic vessels. These lesions the development of which represents a recessive characteristic, are identical with those of hereditary hemorrhagic telangiectasia, in which condition their development represents a dominant characteristic.

The hepatic disease is usually chronic, with cirrhosis and atrophy of the hepatic parenchyma predominating. Alcohol, arsenic and syphilis are associated factors.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1938

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The notable events of the year in neuropsychiatry are not as much related to the scientific aspects as to the editorial aspects of the field. Four new journals have appeared in America, and there are reports that two more may be launched. *Psychiatry*, a "journal of the biology and the pathology of interpersonal relations," is published in Washington as a memorial to William A. White. As its name implies, it is concerned largely with the dynamics of psychology in a broad way. *Epilepsia* has been reborn, after a lapse of almost twenty-five years, under the guidance of William G. Lennox in this country. The *Journal of Neurophysiology*, edited by Dusser de Barenne, Fulton and Gerard, fills a long felt need. *Confina Neurologica* was started by Spiegel and his colleagues in Philadelphia to report advances in "borderland neurology," i.e., the relation of surgery, otology, laryngology, ophthalmology, syphilology and endocrinology to the nervous system. Only one year older is the pioneer of the west coast, the *Bulletin of the Los Angeles Neurological Society*. All this indicates a great increase in neurologic and psychiatric research and a need for publication facilities by an ever increasing number of investigators.

CEREBRAL CIRCULATION

During the past fifteen years there has been a great deal of research work on the circulation of the brain. This was stimulated by the clinical observations and speculations of a century or more, for physicians have long been explaining many symptoms—headaches, fits, transient hemiplegia and aphasia, syncope and hypertension—on the basis of temporary cerebral anemia. At a meeting of the Association for Research in Nervous and Mental Disease in New York in December 1937 a symposium was held on the circulation of the brain and spinal cord. This is reported at length in the proceedings of the society published in 1938, entitled "Circulation of the Brain and Spinal Cord" which will be referred to frequently in this review.

The anatomy of the blood supply to the human brain is unlike that of any other organ. The main arterial supply, coming through the vertebral and the internal carotid arteries enters the circle of Willis

and thus is distributed to all six cerebral trunks. The sharp bend of the internal carotid artery about the body of the sphenoid bone serves to moderate slightly the more violent fluctuations of pressure, such as may occur in aortic disease with hypertension. The circle of Willis is a protective mechanism of great importance, insuring cerebral blood supply to both hemispheres even if one carotid artery is occluded, moreover there are anastomoses between the branches of the posterior, middle and anterior cerebral arteries and even between the cerebral branches of the two hemispheres.¹ There are also anastomoses with the external carotid artery, usually by way of the ophthalmic artery.

Histologically, cerebral vessels differ from vessels elsewhere in the body mainly because their inner elastic membrane is thicker than that of the other arteries and as age advances it hypertrophies and divides into two or more laminae. This strengthening of the inner layer of the arterial wall is probably important in the brain because of the weakness of the outer layers. The adventitia is merely a loose network filled with fluid, being limited outwardly by a layer of glia, thus the perivascular space of Virchow and Robin is formed. Around small vessels it is not a clearly defined space, it is more potential than actual, unless distended with fluid. As the vessels become larger and approach the meninges the space is more distinct, at last becoming continuous with the arachnoid space. These perivascular spaces are analogous to the lymphatic ducts of other organs.

The first quantitative studies of the cerebral blood supply were made by Craigie² and have been confirmed by recent workers. White matter has about 200 to 300 mm of capillary length per cubic centimeter of brain substance, while gray matter has from 600 to 1,000 mm. The difference in blood supply is further magnified by the fact that the capillaries are of larger caliber in the white matter, so even less blood is exposed to the capillary wall—for the smaller the capillary, the greater the amount of blood that comes in contact with the wall of the vessel and the greater the metabolic exchange between blood stream and tissue. Finley's³ excellent preparations show the relative difference in the capillary supply of nuclei, cortex and white matter so conspicuously that one does not need quantitative estimates to be convinced. The most vascular parts of the gray matter are the paraventricular and supraoptic nuclei, but even these have only about one-fifth as rich a capillary bed as has

1 Fay, T. Cerebral Vasculature. Preliminary Report of Study by Means of Roentgen Ray, *J. A. M. A.* **84** 1727 (June 6) 1925.

2 Craigie, E. H. *J. Comp. Neurol.* **31** 429, 1920, *A. Research Nerv. & Ment. Dis., Proc.* **18** 3, 1938.

3 Finley, K. *A. Research Nerv. & Ment. Dis., Proc.* **18** 94, 1938.

skeletal muscle⁴ Wolff⁵ has shown that capillary density is correlated not merely with the number of nerve cells in a given region but with the surface area of these nerve cells, nerve cells with few dendrites have less capillary network around them than nerve cells with many dendrites. This anatomic observation corroborates Gerard's⁶ general thesis that the number of capillaries in a given region is roughly proportional to the oxygen consumption.

CEREBRAL THROMBOSIS

There have been much discussion and much misunderstanding concerning the question of end arteries in the brain. Cohnheim,⁷ the originator of the end artery theory, has been repeatedly quoted and often misunderstood. Part of the confusion has arisen from the fact that different laboratory animals have been used and comparisons have been made with man. Wislocki⁸ has shown that in the opossum there are simple and complete end arteries, even down to the capillary loops. The vascular architecture in cats, rabbits and monkeys more closely approximates that found in human brains. Campbell⁹ gives the most accurate observations available at present. He shows that in the cat, anastomoses do occur between larger arteries. They are found most frequently near the periphery of the arterial trees, especially between branches in the pia. Here the connecting arteries are from 70 to 90 microns in diameter. These arteries are important since they are the ones that directly supply the cortical gray matter. Few of the penetrating arteries anastomose with each other until they reach precapillary size. In the striatum and white matter, anastomosis between arteries is less common.

Cohnheim apparently knew that there are capillary anastomosis in the brain and some connection between the pial vessels, but he underestimated the amount and stated that if such connections do occur they are of no functional importance. Recent animal experiments show that anastomoses between arteries are common and are of importance in saving the brain from small infarctions, even though the collateral blood supply is not enough to obviate larger infarcts. Putnam's¹⁰ demonstration of small areas of reaction or necrosis around minute thrombi in the brain emphasizes the importance of these connections between arteries.

4 Cobb, S, and Talbott, J H. *Tr. A. Am. Physicians* **42** 255, 1927.

5 Wolff, H G, and Dunning, H S. *J. Comp. Neurol.* **67** 433, 1937.

6 Gerard, R W. *A. Research Nerv. & Ment. Dis., Proc.* **18** 316, 1938.

7 Cohnheim, J. *Untersuchungen über die embolischen Prozesse*, Berlin, A. Hirschwald, 1872.

8 Wislocki, G, and Campbell, A C P. *Anat. Rec.* **67** 177, 1937.

9 Campbell, A C P. *A. Research Nerv. & Ment. Dis., Proc.* **18** 69, 1938.

10 Putnam, T J, and Alexander, L. *A. Research Nerv. & Ment. Dis., Proc.* **18** 544, 1938.

and between veins Alexander and Putnam¹¹ point out that the vulnerability of the brain to lack of oxygen and its lack of ability to repair damage are the important things to consider. The peculiarities of the blood supply must be taken into account, but are important only when related to the special reactions of the cerebral tissues. Thus focal anemia is one of the important causes of cerebral lesions.

The mechanism of gross infarction is fairly well understood. While the question of the effect of arterial spasm remains unsolved, the effects of small vascular obstructions are definitely recognizable, such lesions probably cause a number of "diseases," many of them having heretofore been considered "idiopathic" or mysterious. Hemorrhagic necrosis, encephalomalacia, some kinds of encephalopathy and some types of perivascular hemorrhage are probably varying degrees of red and white infarction. Evans¹² thinks the varying degree and the varying suddenness of oxygen deprivation are more important. A red infarct is formed when the circulation is merely slowed, sudden complete occlusion leads to white necrosis and cyst formation. All infarcts at first show some diapedesis of red blood cells and only later grow truly white.

APOPLEXY

Numerous theories have been advanced to explain cerebral hemorrhage. The simplest and oldest is that the vessel wall is weakened by senile changes or disease and that the blood pressure inside the artery ruptures the pathologic wall. Charcot¹³ believed that "miliary aneurysms" are common and that their rupture causes many hemorrhages. Bohne,¹⁴ Globus¹⁵ and others have supported the thesis that gross cerebral hemorrhage takes place only from vessels that lie in softened brain substance. This theory seems to me not only unproved but unreasonable. If, as Globus described it, partial softening of brain substance does take place about arteries, the fluid and soft substance would surround the vessel at a pressure practically as great as that of the normal tissue, i. e., 150 mm of water, whereas the pressure within the artery would be about 1,500 mm of water. It is apparent that what keeps the blood from bursting out is not the support of the surrounding brain tissue or fluid but the elastic and muscular coats of the arterial wall. These coats, as has already been mentioned, have a somewhat different arrangement in cerebral arteries from that in arteries elsewhere in the body. The

11 Alexander, L., and Putnam, T. J. *A Research Nerv & Ment Dis*, Proc **18** 471, 1938.

12 Evans, J. P., and McEachern, D. *A Research Nerv & Ment Dis*, Proc **18** 379, 1938.

13 Charcot, J. M., and Bouchard, C. *Arch de physiol norm et path* **1** 110, 643 and 725, 1868.

14 Bohne, C. *Beitr z path Anat u z allg Path* **78** 270, 1927.

15 Globus, J. H. *A Research Nerv & Ment Dis*, Proc **18** 438, 1938.

strength of the wall is particularly dependent on the inner elastic lamina, and as age advances this lamina hypertrophies and splits up¹⁶ Degenerative processes often weaken this wall, and hemorrhage is the simple result of bursting Of course an aneurysmal dilatation may form before the rupture, but I doubt if congenital aneurysm without degenerative disease is a common cause of cerebral hemorrhage

Merritt and Aring¹⁷ discuss the differential diagnosis of cerebral hemorrhage and thrombosis They believe that it is of more than academic significance, because the immediate prognosis for life and the ultimate prognosis for return of function are different in these cases Also the possibility of surgical intervention and removal of the clot, which has been suggested by several neurosurgeons,¹⁸ enhances the significance of the diagnosis Factors which have significance in regard to the differential diagnosis and which point to the diagnosis of cerebral hemorrhage are

- 1 Onset with headache and vomiting
- 2 Onset with convulsions—especially if syphilis can be excluded
- 3 Stiffness of the neck and Kernig's sign
- 4 Dilatation of the pupil on the side opposite the lesion, or bilateral absence of the light reflex
- 5 Conjugate deviation of the head and eyes
- 6 A bilateral Babinski reflex
- 7 Progression of the focal symptoms over a period of twelve to fourteen hours
- 8 Leukocytosis, with counts of over 12,000 per cubic millimeter
- 9 A cerebrospinal fluid pressure greater than 350 or 400 mm, regardless of whether the fluid is bloody or not
- 10 A bloody cerebrospinal fluid with a xanthochromic supernatant fluid
- 11 A clear or slightly yellow cerebrospinal fluid with pleocytosis (more than 100 cells per cubic millimeter), when syphilis and septic embolus can be excluded

A false statement often found in the literature and more often quoted is that the signs and symptoms of cerebral thrombosis frequently develop slowly The slow development of focal symptoms (hemiplegia, aphasia

16 Hackel, W M Virchows Arch f path Anat **266** 630, 1928

17 Merritt, H H, and Aring, C D A Research Nerv & Ment Dis, Proc **18** 682, 1938

18 Bagley, C, Jr Spontaneous Cerebral Hemorrhage Discussion of Four Types, with Surgical Considerations, Arch Neurol & Psychiat **27** 1133 (May) 1932 Penfield, W Canad M A J **28** 369, 1933 Craig, W M, and Adson, A W Spontaneous Intercerebral Hemorrhage Etiology and Surgical Treatment, with Report of Nine Cases, Arch Neurol & Psychiat **35** 701 (April) 1936

and hemianopia) occurs so rarely, if at all, in cases of cerebral vascular lesions that such a diagnosis is extremely hazardous¹⁹ This is especially true for patients with a normal blood pressure and normally functioning kidneys In such cases an examination of the cerebrospinal fluid is of great importance, since an expanding lesion may cause an increase in the cerebrospinal fluid pressure which can be detected before the development of choked disks

For patients with cerebral vascular accidents who die and are studied post mortem the clinical diagnosis usually is "hemorrhage," but at least half of them show "softening," i e, thrombosis with infarction The clinical studies of Merritt and Aring show that probably only one fifth of the vascular accidents in which death does not occur can be attributed to hemorrhage, the remaining 80 per cent being due to thrombosis and rarely embolus

Experiments by Schmidt,²⁰ Pool,²¹ Thomas²² and others have shown that carbon dioxide, glyceryl trinitrate, acetylcholine, ether and alcohol are the best cerebral vasodilators It seems to me that they should be used therapeutically early in cases of cerebral thrombosis because restoration of circulation to an infarcted area within a few hours of the onset will probably save a great deal of function that will be permanently lost if the orthodox treatment of rest and morphine is followed In fact, I consider morphine as probably harmful in such cases I would rather have the patient kept awake, with his blood pressure up and his head moderately raised Caffeine in large doses may cause vasoconstriction, so it should be used with caution if at all

REGULATION OF THE CEREBRAL BLOOD SUPPLY

In the vertebrate organism there are two main integrating systems—the blood stream and the nerves These two reach every part of every living organ Between these two principal integrators there is a reciprocal relation that is of great importance The brain, like every other organ, is dependent on its blood supply, but the blood supply is dependent on a normally functioning brain, for blood flow to the various organs, even to the brain itself, is largely regulated by the vasomotor centers of the brain and spinal cord (see the accompanying diagram) The central nervous system contains the head ganglions of the autonomic nervous

19 Merritt, H H, in Blumer, G The Practitioners Library of Medicine and Surgery, New York, D Appleton-Century Company, Inc, 1936, vol 9, chap 23

20 Schmidt, C F, and Hendrix, J P A Research Nerv & Ment Dis, Proc 18 229, 1938

21 Pool, J L, Nason, G I, and Forbes, H S Cerebral Circulation Effect of Nerve Stimulation and Various Drugs on the Vessels of the Dura Mater, Arch Neurol & Psychiat 32 1202 (Dec) 1934

22 Thomas, C B Cerebral Circulation Effect of Alcohol on the Cerebral Vessels, Arch Neurol & Psychiat 38 321 (Aug) 1937

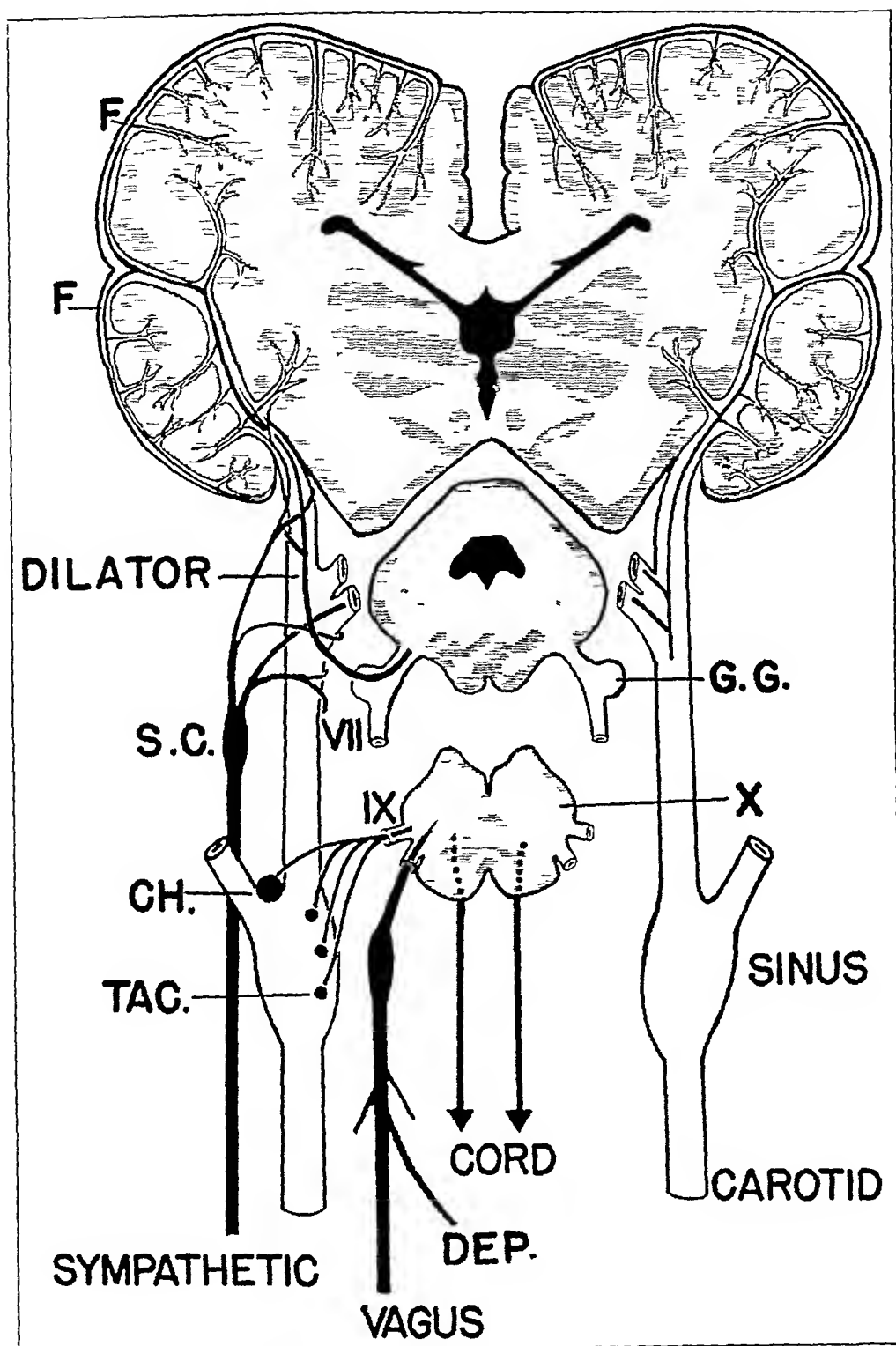


Diagram of the physiologic mechanisms concerned in maintaining the blood flow to the brain

system, which in turn control the vegetative nerves to the heart and vessels. Thus a lesion in the heart and a lesion in the hindbrain are equally lethal.

The extracerebral control of cerebral circulation has been worked out carefully by Heymans²³ and his co-workers²⁴ in a series of classic experiments. Weiss²⁵ summarizes this work and describes his own contributions to the subject. He says that the circulation of the brain acts like that of an organ with continuous maximal activity, it must be served, even at the expense of other organs. To maintain this all-important blood supply at a relatively constant rate there are several physiologic mechanisms. These are indicated in the accompanying diagram.

The principal regulator of the amount of blood that flows to the brain is the blood pressure in the carotid and vertebral arteries. In man the vertebral arteries are relatively small, and the carotid arteries control most of the circulation to the cerebrum, so the carotid sinus mechanism is most important. In the wall of this sinus at the bifurcation of the external and internal carotid arteries lies a structure with sinusoidal apertures that are bathed in the blood that enters the sinus. Nerve endings in this structure (*CH* in the figure) are sensitive to changes in carbon dioxide tension. If the content is high, impulses from this chemical end organ pass along the carotid sinus nerve to the hypoglossal root (*IX* in the figure) in the medulla oblongata, and there reflexly increase the blood pressure via the vasomotor center and the pathways to the spinal cord. Small tactile (*Tac*) organs that lie in the wall of the carotid sinus respond to stretching or contraction of the wall. If the wall is stretched, impulses go to one of the medullary centers of the vagus nerve (*X*) and thence reflexly lower the blood pressure via both the vagus nerve and the vasodilator mechanism of the spinal cord. Contraction of the wall of the sinus has the opposite effect. Similar organs that register stretch are found in other vessels, for example the aorta. Impulses from this source travel along the aortic depressor nerve (*DEP*) and reflexly lower the blood pressure. The vagus nerve itself contains both afferent and efferent fibers of the heart and other viscera, so vagovagal reflexes can also control the blood pressure. Such briefly, is the extracerebral control of the blood supply to the brain.

Within the skull there is an intrinsic or cerebral control. Penfield²⁶ and Forbes²⁷ have shown that the cerebral vessels have both a vaso-

23 Heymans, C. *Bruxelles-med* **16** 1411, 1936.

24 Bouchaert, J. J., and Jordan, F. *Rev. belge sc. med.* **9** 12, 1937.

25 Weiss, S. *A. Research Nerv. & Ment. Dis., Proc.* **18** 571, 1938.

26 Chorobski, J., and Penfield, W. *Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, with Observations on the Pial and the Intracerebral Plexus*, *Arch. Neurol. & Psychiat.* **28** 1257 (Dec.) 1932.

27 Forbes, H. S., and Cobb, S. *A. Research Nerv. & Ment. Dis. Proc.* **18** 201, 1938.

constrictor and a vasodilator innervation. The fine fibers (*F*) that follow the smaller vessels seem to have a vasomotor function. By physiologic experiments on cats, rabbits and monkeys, vasoconstrictor nerves have been proved to be present on vessels of the parietal cortex²⁷ and basal ganglia.²⁸ The constriction of arteries which follows stimulation of these nerves is only about one-tenth as great as the constriction of arteries of a similar size in the skin and other extracranial organs. The vasoconstrictor innervation reaches the brain by way of the cervical sympathetic nerves and the superior cervical ganglion (*SC*).

I do not believe with Ricker²⁹ that the nervous control of the vessels plays much of a role in the causation of cerebral lesions. There is fairly good clinical evidence that cerebral vessels may contract in a spasmodic way and cause temporary symptoms, but Forbes²⁷ has shown that the control is slight under normal conditions. In scars and sclerotic areas the vasomotor nerves may have a lowered threshold which predisposes the vessels to spasmodic constriction and anoxia of the tissue.

Vasodilator nerves have also been found on cerebral vessels of the parietal cortex. Stimulation experiments²⁷ have shown that these fibers leave the hindbrain with the facial nerve and pass to the geniculate ganglion (*GG*) along the great superficial petrosal nerve and thence to the carotid artery and its branches.

Fog³⁰ and Forbes³¹ independently demonstrated that if the systemic blood pressure of an animal is made to fall, from whatever cause, to a low level, the arteries of the pia will dilate rapidly and widely. In the cat the critical level of systolic blood pressure at which this usually occurs is about 60 mm. of mercury. The immediate cause of arterial dilatation seems to be the sudden slowing of the blood flow which obviously follows the drop in pressure and can be seen in the living vessels under the microscope. The importance of this phenomenon cannot yet be estimated, but it must partly compensate for the decreased cerebral blood flow of a failing circulation. Moreover, it may occur in other organs, although it has been observed only in the brain.

With so many regulatory mechanisms one might expect frequent changes in the caliber of the vessels and in the blood flow, but the flow is remarkable for its steadiness.³² The constant temperature of the

28 Schmidt, C. F. *Am. J. Physiol.* **110** 137, 1934.

29 Ricker, G. *Sklerose und Hypertonie der innervierten Arterien*, Berlin, Julius Springer, 1927, p. 193.

30 Fog, M. *Cerebral Circulation: Reaction of the Pial Arteries to a Fall in Blood Pressure*, *Arch. Neurol. & Psychiat.* **37** 351 (Feb.) 1937.

31 Forbes, H. S., Nason, G. I., and Wortman, R. C. *Cerebral Circulation: Vasodilation in the Pia Following Stimulation of the Vagus, Aortic and Carotid Sinus Nerves*, *Arch. Neurol. & Psychiat.* **37** 334 (Feb.) 1937.

32 Lennox, W. G. *Constancy of the Cerebral Blood Flow*, *Arch. Neurol. & Psychiat.* **36** 375 (Aug.) 1936.

brain, the "closed box" arrangement, the mixture of blood by anastomosis, the governing action of carbon dioxide, the moderating reflexes from vagodepressor nerves and the carotid sinus, and the paucity of direct vasomotor control, all tend to make the cerebral blood flow constant. The fact that it does not fluctuate much under physiologic conditions may be explained teleologically by assuming that delicate nerve tissue requires a steady supply of oxygen rather than a rich one. This supposition is reasonable because there is evidence that a rapid change in the environment of nerve cells is more harmful than a slow but more extensive change. Probably a constant supply of oxygen to the brain is more important than an exceptionally rich one, so the brain as a whole has a steady blood flow. The lower centers in the brain stem, being active throughout life at all times, need an even, continuous flow, for on them vital functions depend. The cerebral hemispheres, however, being more specialized and less continuously active, have a less steady blood flow, and those parts of the cerebral cortex most actively functioning at any given time have temporary and local changes in blood flow.⁶

Lennox, Gibbs and Gibbs³³ succinctly state the important point about the regulation of circulation in the brain when they say that gross changes in total cerebral flow probably are not adjustments to nutritional requirements of the brain cells but are directed toward the maintenance of a constant tension of carbon dioxide and a constant hydrogen ion concentration in the nerve cells. Changes in blood flow as a result of alterations in metabolic activity are probably local. According to these authors, the unique characteristic of the cerebral blood flow as compared to the blood flow in other organs is that it is steady, showing little variation.

SYNCOPE, CONVULSIONS AND MIGRAINE

Syncope from various causes is discussed by Lennox, Gibbs and Gibbs³³ as well as by Weiss²⁵. In most cases it is due to some fundamental circulatory change—cardiac inhibition, failure of the heart or vasodilatation, each may cause ischemia of the brain and fainting. The group of cases in which no failure of circulation is observable might be explained by vasoconstriction in the brain, but the evidence is against this explanation. In the first place, the loss of consciousness comes on too suddenly to be readily explained by such a mechanism, and, secondly, no change in total cerebral blood flow is observable. Since I do not believe that consciousness is controlled by centers which can be switched on and off by reflex neural discharges, the remaining possibility seems to be that stimuli from local areas of ischemia from stimulation of end organs in the carotid sinus, heart and great vessels may induce discharges of neurons in the cerebral cortex which spread like the epileptic dis-

³³ Lennox, W. G., Gibbs, F. A., and Gibbs, E. L. *A Research Nerv & Ment Dis*, Proc **18** 277, 1938.

charge and blot out consciousness in a few seconds. The similarity of this syndrome, as described by Weiss, to an epileptic fit may be striking.

Another set of causes of unconsciousness is discussed by Lennox, Gibbs and Gibbs,³² who wisely avoid definition of the term and speak generally of 'cerebral activity' and its cessation. They point out that the patient ceases to respond to stimuli when the oxygen content of the blood falls to a point between 30 and 24 per cent of saturation. Sugar is the other constituent of the blood about which data are available. When there is less than 30 mg. of sugar per hundred cubic centimeters of blood, coma and convulsions may supervene.

Many convulsions are caused by asphyxia and vascular disorders, but recent work shows that epileptic seizures are not often caused by widespread vascular changes within the brain. There are many clinical observations that show that ischemia causes discharge in the central nervous system (fits). Seizures due to heart block, cerebral infarct, strangulation, cyanide, metrazol and insulin poisoning and certain other factors closely resemble the fits that are ascribed to 'cerebral vascular spasm'. Oxygen deficiency in the cells of the brain is doubtless one of the commonest causes of convulsions. But that does not mean that widespread spasm of the arteries is present. On the other hand, local vasospasm cannot now be disregarded as one cause of epileptiform seizures, and the proof that there is vasomotor innervation of the cerebral vessels makes such a mechanism one of the probable causes of certain types of seizures.

Penfield³⁴ finds at operation many abnormalities of the cerebral circulation, but none that appears to be causative of the seizures. The fit seems to leave behind it a more or less local area of overstimulated brain which, because of its overactivity, shows local dilatation of vessels and a rapid blood flow. The commonest phenomenon observed is the cessation of visible pulsation in the cerebral arteries during a seizure.

The headaches supposed to be due to vascular disturbances in the brain, both typically migrainous and miscellaneous, are explained by Wolff and Graham on the basis of changes in pulse pressure in the extracerebral vessels. Experiments on patients with ergotamine tartrate and histamine have led to a great advance in the treatment of migraine, a common and incapacitating disease. The report by Graham and Wolff³⁵ on their investigations and on the work of others is one of the most encouraging contributions to the symposium. An accurate knowledge of the action of ergotamine is of prime importance to the study of migraine, and the difference in physiologic effect reported by the different experi-

34 Penfield, W. A. Research Nerv. & Ment. Dis., Proc. **18** 605, 1938.

35 Graham, J., and Wolff, H. G. A. Research Nerv. & Ment. Dis., Proc. **18** 638, 1938.

menters³⁶ should be the subject of further study. The cause of headache, however, is far from settled. Penfield³⁷ and McNaughton³⁸ describe sensory fibers from the trigeminal nerve to the dural sinuses; they have observed pain similar to migraine caused by traction on the veins that enter the sinuses.

ALCOHOLISM

Five years ago it was almost universally believed that the lesions and symptoms caused by chronic alcoholism were due to the toxic effect of alcohol itself. The pioneer papers of Shattuck³⁹ and Meyer⁴⁰ were scarcely known. Now there is excellent proof⁴¹ that "alcoholic neuritis" is caused by lack of vitamin B₁, and there is good evidence that "Korsakoff's psychosis" and "alcoholic hallucinosis" are merely clinical variants of pellagra⁴². Thus the treatment of these syndromes has changed from a vague "supportive" regimen to specific therapy with large amounts of vitamin. 20 to 40 mg of crystalline vitamin B₁ (or its equivalent) for alcoholic neuritis and for hallucinosis, memory defect, glossitis and erythema. Recently vitamin C has also been found to be deficient in patients with chronic alcoholism. Plaut⁴³ reported a low content in the blood and spinal fluid of a few patients, and Alexander and his associates⁴⁴ have studied 106 alcoholic addicts. The evidence is definite that vitamin C is at an abnormally low level (averaging about half the normal value), but whether or not this deficiency is important or incidental is not yet known, although scurvy is not uncommon in alcoholic addicts. The propensity of these persons to have subdural hematomas may be due to the scorbutic friability of the blood vessels⁴⁵. It has been suggested that the hemorrhagic lesions of the midbrain in cases of Weirnicke's "polioencephalitis" might be due to scurvy, but

36 Pool, L. J., and Nason, G. I. Cerebral Circulation. Comparative Effect of Ergotamine Tartrate on the Arteries in the Pia, Dura and Skin of Cats. *Arch Neurol & Psychiat* **33** 276 (Feb.) 1935. Schmidt and Hendrix²⁰

37 Penfield, W. *Proc Am Neurol A*, 1938, to be published.

38 McNaughton, F. L. A Research Nerv & Ment Dis, *Proc* **18** 178, 1938.

39 Shattuck, G. C. *Am J Trop Med* **8** 539, 1928.

40 Meyer, A. *Schweiz med Wchnschr* **2** 1243, 1932.

41 Romano, J. *Am J M Sc* **194** 45, 1937. Goodhart, R., and Jolliffe, N. Effects of Vitamin B (B₁) Therapy on the Polyneuritis of Alcohol Addicts, *J A M A* **110** 414 (Feb 5) 1938.

42 Spies, T. D., and Cooper, C. *Internat Clin* **4** 1, 1937.

43 Plaut, F., and Bulow, M. *Ztschr f d ges Neurol u Psychiat* **152** 84, 1935.

44 Alexander, L., Pijoan, M., Schube, P. G., and Moore, M. Cevitamic Acid Content of Blood Plasma in Alcoholic Psychoses, *Arch Neurol & Psychiat* **40** 58 (July) 1938.

45 Ingalls, T. H. *New England J Med* **215** 1279, 1936.

Recent experiments of Alexander, Pijoan and Myerson⁴⁶ have shown that these lesions are due to lack of vitamin B₁.

The treatment of delirium tremens also has been improved greatly. In the past it has often been stated that the use of alcohol should be continued, for the delirium is due to the sudden cessation of drinking. These beliefs, which never had a sound clinical basis, have now been thoroughly controverted by Pike,⁴⁷ who found that in 205 of 275 patients with delirium tremens, delirium developed while they were still drinking. The theory that the patient should be dehydrated because he may have cerebral edema ("a wet brain") has also been satisfactorily thrown into the discard. Nicholson and Taylor⁴⁸ have shown that alcohol causes diuresis with retention of potassium which rapidly dehydrates the body and may cause most of the symptoms of the alcoholic "hangover." It is well known that water is greatly craved some hours after a debauch. It has also been demonstrated by Thomas, Semrad and Schwab⁴⁹ that the amount of total protein in the serum is greatly reduced in patients with delirium tremens. These authors have demonstrated the fact that patients with delirium tremens improve more rapidly if the intake of fluid is drastically increased. A liter of physiologic solution of sodium chloride should be given parenterally as soon as possible, and saline solution and other fluids should be given by mouth until at least 3,000 cc is ingested per day. All vitamins should be given in large amounts, especially B₁. Paraldehyde is the best sedative. With such a regimen the delirium can be shortened and lives can be saved. Lumbar puncture is useful in respect to the diagnosis, to indicate whether or not there is evidence of injury to the brain, but it is not important therapeutically.

SCHIZOPHRENIA

In the review of neuropsychiatry for 1937 I⁵¹ discussed at length the status of the insulin treatment of schizophrenia. Since then the treatment has been applied to hundreds of patients in various state and private hospitals. The initial enthusiasm is beginning to wane. Critical judgment of the results indicate that treatment with insulin and with metrazol certainly has value and often brings about a remarkable remis-

46 Alexander, L., Pijoan, M., and Myerson, A. *Tr Am Neurol A*, 1938, to be published.

47 Pike, D. *Am J Psychiat* **93** 1387, 1937.

48 Nicholson, W. M., and Taylor, H. M. *J Clin Investigation* **17** 279, 1938.

49 Thomas, J., Semrad, E. V., and Schwab, S. M. *Am J M Sc* **195** 820, 1938.

50 Footnote deleted by the author.

51 Cobb, S. Review of Neuropsychiatry for 1937, *Arch Int Med* **60** 1098 (Dec) 1937.

sion of symptoms, nevertheless many patients have a relapse, and many would have had remissions anyway. The data are well summarized by Paskind,⁵² Malzberg⁵³ and Ross⁵⁴. The general consensus appears to be that both procedures constitute a distinct contribution to the treatment of schizophrenia, though few workers now report the astonishingly high rates of remission which were claimed in some of the earlier papers. Reports are also appearing which suggest that metrazol may be of value for patients with depressive reactions⁵⁵. The value of the proper psychotherapeutic management of the patient, particularly during treatment with insulin, is still stressed. An interesting technical development consists of the recognition of the therapeutic value of prolonged coma, i. e., reactions varying between coma and twilight states and lasting over several days.

The death rate associated with both forms of therapy remains low, the most prevalent causes associated with insulin therapy being cardiac collapse and pulmonary edema. With metrazol therapy, pulmonary complications, particularly aspiration pneumonia, are the most frequent causes of death. A great deal of investigative work has been reported. From a number of sources it appears that the major effects of both types of therapy are on the oxygen consumption of the central nervous system and on the autonomic nervous system. Attempts to duplicate the therapeutic results by exposure to low oxygen tensions have been unsuccessful, and attention at present is turned to the autonomic nervous system as the key to the therapeutic mechanisms.

A trend in this treatment that gives pause to the careful physician is the use of other convulsant drugs, either alone or combined with insulin, when insulin alone does not work. As I mentioned last year camphor and metrazol⁵⁶ have been used in this way. These mixtures of drugs makes one lose hope that any specific treatment for schizophrenia has been found. Probably some severe general reaction in the brain, like anoxia, is the therapeutic agent.

The question of whether permanent damage to the brain results from the use of either insulin or metrazol has been actively debated during the last year. Many, although not all, animal experiments have shown that extensive damage, usually accompanied by multiple areas of hemorrhage

52 Paskind, H. A., in Reese, H. H., Paskind, H. A., and Sevringhaus, E. L. Yearbook of Neurology, Psychiatry and Endocrinology for 1937, Chicago, The Year Book Publishers, Inc., 1938.

53 Malzberg, B. Psychiatric Quart. **12** 528, 1938.

54 Ross, J. R. A Statistical Study of Results in the New York State Hospitals, read before the American Psychiatric Association, San Francisco, June 9, 1938.

55 Low, A. A., Sonenthal, I. R., Blaurock, M. D., Kaplan, M., and Sherman, I. Metrazol Shock Treatment of "Functional" Psychoses, Arch. Neurol. & Psychiat. **39** 717 (April) 1938.

56 von Meduna, L. Ztschr. f. d. ges. Neurol. u. Psychiat. **152** 235, 1935.

may occur after both types of therapy, and in a certain number of patients dying from the treatments, comparable lesions have been observed. There is some clinical evidence which suggests that damage of an irreversible nature occurs in the brain, but the fine changes in higher functions seen after damage to the frontal lobe have not yet been found in patients treated with either insulin or metrazol. Nevertheless, it is notoriously difficult to make an estimate of these finer mental functions, especially when the patient was not examined before his illness.

It is particularly alarming to learn, on the good authority of Weil's⁵⁷ experiments, that insulin given to animals, in doses comparable to those used for human beings, causes widespread degeneration and necrosis of the ganglion cells of the brain. These well controlled experiments indicate that the damage is caused by the cumulative effect of repeated large doses of insulin.

Other convulsants, such as thujone and camphor, have been shown⁵⁸ to cause lesions in the cerebral cortex, consisting of chromatolysis or even necrobiosis of the ganglion cells and petechial hemorrhages. Little work has been done on the effects of metrazol on cerebral ganglion cells, but at the last meeting of the American Neurological Association, Alpers⁵⁹ presented data on 7 monkeys which had been given convulsive doses of metrazol. Three brains were normal, and 4 showed cell changes, 3 of these having subarachnoid hemorrhages.

Such evidence makes me believe that the therapeutic effect of insulin and metrazol may be due to the destruction of great numbers of nerve cells in the cerebral cortex. This destruction is irreparable. The therapy may be justifiable in cases of schizophrenia if experience proves that treatment results in permanent improvement, but the physician recommending these radical measures should do so with his eyes open to the fact that he may be removing symptoms by practically destroying the most highly organized part of the brain. The use of these measures in the treatment of psychoses and neuroses from which recovery may occur seems to me entirely unjustifiable.

New light has been thrown on the etiology of psychoses by Elvidge,⁶⁰ of the Montreal Neurological Institute. For several years he has been

57 Weil, A., Liebert, E., and Heilbrunn, G. Histopathologic Changes in the Brain in Experimental Hyperinsulinism, *Arch Neurol & Psychiat* **39** 467 (March) 1938.

58 Oppen, L. The Pathology of Thujone and Monobromated Camphor Convulsions Compared with the Pathology of Human Epilepsy, *Arch Neurol & Psychiat*, to be published.

59 Strecker, E. A., Alpers, B. J., Flaherty, J. A., and Hughes, J. *Tr Am Neurol A*, 1938, to be published.

60 Elvidge, A. R., and Reed, G. E. Biopsy Studies of Cerebral Pathologic Changes in Schizophrenia and Manic-Depressive Psychosis, *Arch Neurol & Psychiat* **40** 227 (Aug) 1938.

carefully studying biopsy specimens from the brains of patients with schizophrenia and manic-depressive psychosis. For years pathologists have searched in vain for significant changes in the brains of patients who die while suffering from these diseases. Now Elvidge and his colleagues have shown that changes do occur in the oligodendroglia and that these can be demonstrated in specimens taken during life and fixed immediately for staining by the Hortega method. The oligodendroglia cells were found to be swollen, with shortened processes, and the nuclei were either normal or pyknotic. All but 1 of 13 patients with typical schizophrenic syndromes showed definite swelling of the oligodendroglia, another showed it on one occasion but not on reexamination a year later. Specimens from the brains of 5 patients with manic-depressive psychoses all showed swelling, although in 1 patient it was slight. The control material used was large, because Elvidge had access to specimens taken at many operations. It is significant that in this material swollen oligodendroglia cells were observed in several specimens from patients operated on for convulsions, and these appeared to be the patients who had stupor or other mental symptoms at the time of operation. This suggests that the histologic changes observed may not be specifically related to schizophrenia or manic-depressive psychosis but to the presence of any abnormal mental state. The observations are important and should be carried out extensively and with many controls. When skilfully performed, there is no reason to suppose that removal of biopsy specimens from the cortex does harm to cerebral function. In fact, I think it a less harmful procedure than the production of one therapeutic convulsion.

SCIATICA

It has long been suspected by clinicians that pain in the sciatic nerve is usually due to mechanical difficulties in the sacrum and lower portion of the spine and that it had little to do with "neuritis." The work of orthopedic surgeons along conservative lines has helped many patients. Then more radical procedures, such as arthrodesis,⁶¹ were tried, and they proved their worth by the cure of many patients with stubborn sciatica. Now neurosurgical procedures are taking their place in the treatment of this common and incapacitating disorder. As early as 1911 Middleton and Teacher⁶² described pressure on the spinal cord by protrusion of the intervertebral disk, but it was considered a rare condition. Not until 1937 was it clearly demonstrated, by Barr and Mixter,⁶³

61 Smith-Petersen, M. N., and Rogers, W. A. Arthrodesis for Tuberculosis of the Sacro-Iliac Joint. Study of End-Results, *J. A. M. A.* **86** 26 (Jan 2) 1926.

62 Middleton, G. S., and Teacher, J. H. *Glasgow M. J.* **76** 1, 1911.

63 (a) Barr, J. S. *J. Bone & Joint Surg.* **19** 323, 1937. (b) Mixter, W. J. *Ann. Surg.* **106** 777, 1937. (c) Barr, J. S., Hampton, A. O., and Mixter, W. J. Pain Low in the Back and "Sciatica" Due to Lesions of the Intervertebral Disks, *J. A. M. A.* **109** 1265 (Oct 16) 1937.

that a certain number of cases of "sciatica" are caused by this lesion in the lumbar portion of the spine. Pain, starting in the back and spreading down the thigh and outer side of the leg, even in the ankle, is the presenting symptom. The pain is severe and lancinating and is brought on by bending and lifting. There is limitation of motion of the lower part of the back and in extension of the affected leg. The ankle jerk on this side may be diminished or absent. Sometimes roentgenograms show narrowing of the intervertebral disk, and three fourths of the patients have a slightly increased protein content of the spinal fluid. Diagnosis, however, is not certain until iodized poppyseed oil has been injected into the lumbar sac of the spinal canal and roentgenograms have finally demonstrated the lesion.⁶⁴ If the diagnosis seems certain, laminectomy is performed, and usually a mass is found protruding into the spinal canal between the fourth and the fifth lumbar vertebra. The annulus of the disk has ruptured and made a tumor which presses on some of the roots of the sciatic nerve. In some cases the nucleus pulposus of the disk protrudes through the ruptured annulus making a chalky, fibrous mass. Removal is not difficult if proper exposure can be obtained without trauma to the nerve structures. Mixter^{63b} reports 58 cases of intractable pain in the back, in none of these cases had conservative orthopedic treatment given relief. Diagnosis of rupture of the intervertebral disk was made, and all the patients were subjected to operation. In 32 cases the symptoms were relieved, often immediately, in 14 other cases there was marked improvement. Thus it seems that another vague neurologic entity, "sciatica," is being split up into its elements by careful research, and on the basis of knowledge concerning its causation rational therapy is being administered.

64 Hampton, A. O., and Robinson, J. M. *Am J Roentgenol* **36** 782, 1936

Book Reviews

Clinical and Experimental Investigations in Agranulocytosis By Pieben Plum, M D Pp 410, with 125 illustrations and 42 tables Copenhagen Nyt Nordisk Forlag, 1937

This is an excellent piece of work, which was carried on while the author was working as a research fellow under Prof Valdemar Bie at the Blegdam Hospital in Denmark. It represents an unusually comprehensive study of agranulocytosis based on a careful review of the literature and on 88 cases, all but 1 of the patients coming under the author's observation.

The monograph is a scholarly production. Every detail has been well worked out. The history of agranulocytosis is interestingly gathered together. The clinical description of the disease and its differential diagnosis are clear, logical and concise. The discussion of the possible etiology of the condition is especially interesting. The author argues a strong case against aminopyrine and presents striking figures to show the close parallelism in Denmark from 1926 to 1936 between the sale of aminopyrine, on the one hand, and the number of known cases of agranulocytosis, on the other. He thinks, in the light of present knowledge, that the best form of treatment available is that of prevention, the best prophylaxis is reduction of the use of drugs which appear to injure the formation of leukocytes.

Students of hematology will appreciate the colored and uncolored photographs of marrow and blood films which have been reproduced. They illustrate the author's conception of the type of cell encountered in studies of the bone marrow and demonstrate the practical value of this particular diagnostic method.

The translation of this book into English was done by Dr Hans Andersen. He deserves a compliment for the felicitous manner in which he has presented Danish points of view and concepts to English readers.

Last, but not least, the author appears to be a level-headed investigator with a knack at digesting and evaluating the work of others. His bibliography of 422 recent references to the subject bears witness to his thoroughness. On the whole the volume can be highly recommended to any reader at all interested in diseases of the blood.

Fever Therapy Edited by the Members of the American Committee Pp 486 New York Paul B Hoeber, Inc, 1937

As long ago as 1931 an American conference on fever therapy was held in Rochester, N Y. Other conferences were held each year thereafter and proved interesting. Finally it was decided to hold an international conference on the subject. This took place in New York on three days in March 1937. Physicians from sixteen countries were in attendance. The present volume records abstracts and discussions of the papers presented at that meeting.

The book is not as large as it appears as it is really only 184 pages long. Each abstract, however, is reprinted in English, French and German. The abstracts of the various papers reported are by necessity short, but from them and the ensuing discussion one can obtain at a glance a good deal of information concerning the present international status of fever therapy.

Fever therapy is being employed in a number of diseases, beneficially in some and without obvious benefit in others. Syphilis and gonorrhea, for example, appear often to be benefited by heat, whereas multiple sclerosis does not. The discussions of the various papers are interesting for they show where doubt exists, and one gathers that overenthusiasm is being curbed. On the whole this is an interesting volume worth having in any medical library. It makes a useful handbook for reference.

Approved Laboratory Technic Clinical, Pathological, Bacteriological, Mycological, Parasitological, Serological, Biochemical and Histological By John A. Kolmer, M.D., and Fred Boerner, V.M.D. Second edition. Price, \$8. Pp. 893, with 392 illustrations. New York: D. Appleton-Century Company, Inc., 1938.

The text constitutes an encyclopedia of laboratory procedures and has an enormous scope. Besides covering all clinical laboratory procedures, it discusses the housing, feeding, inoculating, bleeding and autopsy study of animals and the prevention and the emergency treatment of laboratory accidents. The second edition has been thoroughly revised and brought up to date. Five new chapters have been added on methods for the hormonal diagnosis of early pregnancy, hydatidiform mole, chorionepithelioma and teratoma of the testes, on diagnostic mycologic methods, on methods of examination of the skin and mucous membranes for animal parasites, on methods for conducting tests for allergy, and on histologic methods and the preparation of specimens for museums. The new chapter on mycology and the increased amount of material devoted to parasitology are to be welcomed. The chapters devoted to bacteriologic and serologic procedures are especially fine. The illustrations are plentiful and well chosen. In this edition the new colored plates on normal and abnormal blood cells are a definite improvement. The reviewer deplors the almost complete lack of a bibliography in a text of this type, which is, in reality, a compilation of laboratory procedures. An "approved" list of additional references at the close of each chapter, such as that given by Konzelmann after the chapter entitled "Histological Methods and the Preparation of Museum Specimens," would add even greater value to the book.

The book should be invaluable to clinical pathologists, to laboratory technicians and to the practicing physician who must do or supervise his own laboratory work. The absence of discussion of the clinical significance and diagnostic value of the laboratory tests described limits greatly its value as a text for medical students.

Le traitement radiologique de l'actinomyose By Axel Renander. Price, 8 kronor. Pp. 75. Stockholm: P. A. Norstedt & Soner, 1937.

This excellent summary of the radiologic management of actinomycosis describes the results of treatment of 52 patients observed since 1915 in Radiumhemmet, in the Roentgen Institute of the Serafimer Hospital and in the private practice of Dr. G. Forssell. The following lesions were encountered: those of the face and neck in 31 patients, of the abdomen in 13, of the thorax in 3, of the skin in 2, of the genital region in 1 and of undetermined origin in 2. The form of treatment has varied, but currently it consists of roentgen therapy, the application of molded plaques containing radium needles or exposure to a radium bomb, or *télé-radium*. In this series of cases these various techniques were employed singly or in diverse combinations. Roentgen therapy was effected by repeated exposures, totaling one skin erythema dose, daily or on alternate days over a period of from three to twelve days. The intervals between such series was six to eight weeks, and as many courses as necessary were given. The tube, which was operated at 160 to 170 kilovolts, and filters of various sorts were used. The amount of radium applied in the plaque varied from 200 to 1,600 milligram hours but was usually enough to cause a light erythema with some desquamation. The maximum amount of radiation applied by means of the bomb was 56.22 gram hours, although most patients received much less.

The following results were obtained with this treatment: Twenty-one of the patients with actinomycosis of the face and neck were cured, 5 of those with abdominal involvement and both patients with cutaneous lesions recovered. The author demonstrates adequately the value of vigorous roentgen and radium therapy but was unable to state which technic was the more efficacious. It appeared that the traditionally used potassium iodide did not alter appreciably the radiologic results.

The Diary of a Surgeon in the Year 1751-1752 By John Knyveton, Licentiate of the Society of Apothecaries, Doctor of Medicine of the University of Aberdeen, Teacher of Midwifery to Man and Mid-Wife in Infirmary Hall, Surgeons' Mate, H M S Lancaster Edited and transcribed by Ernest Gray Cloth Price, \$2 50 Pp 322, with 9 illustrations from contemporary sources New York D Appleton-Century Company, 1937

This is a delightful book and may be read with a great deal of pleasure not only by the doctor but by any one who cares for early works. The easy flowing style, the miniature word paintings and what the publisher calls a Pepysian flavor add to the charm. One might suspect a familiarity with Pepys were it not for the fact that John Knyveton died while Pepys' journal was still lying about undeciphered.

Nothing much is added to the knowledge of medical history, for physicians are already familiar with the history of the period, but the breezy style and the youthful optimism of the presentation supply a novel vantage point from which to view the period. One of the bright spots of the book is where William Hunter is described as "having a damnable way of never Offering a Suggestion on matters Medico-Physical until he has proved it privately by Experiment beforehand, the which is Highly Exasperating to those that prefer to browse on the Windy Heights of Pure Discourse."

The author recounts his student days, with comments on the activities of the resurrectionists, the bleedings, the clysters, the "laudable pus," the puerperal sepsis and all the things that blessed and cursed this period of medical practice. He dwells a bit on the nonmedical diversions of the medical students of the time.

In connection with his experience as surgeon's mate in the British navy, he discusses scurvy, the treatment of gunshot wounds and injuries aboard ship. He took part in an attack on a pirate ship. Later he was placed in medical charge of an island overrun with yellow fever and became a victim of the disease, but survived.

There was never a dull moment in his life, and the book will entertain all the members of the reader's family and will perhaps mildly shock some of them.

Uric Acid in Blood and Urine By Knud Brøchner-Mortensen Price, 9 kroner Pp 269, with 63 tables, 58 diagrams and 45 protocols Copenhagen Levin & Munksgaard, 1937

This is an excellent piece of work, done, apparently, by the author in connection with his thesis for the degree of Doctor in Medicine at Copenhagen. First written in Danish, it is now printed in English, only the final chapter appearing in both languages. The tables and diagrams which accompany the discussion are easily understood. The translation from Danish to English is admirable.

The author first reviews various methods available for the analysis of the uric acid in blood and urine and points out their most striking faults. Finally he presents new methods of his own devising and describes the technic of their performance in detail.

After a historical account of methods, the remainder of the book is concerned with experiments in which the new methods were utilized. The experiments dealt with uric acid clearance under a variety of circumstances, under conditions in which the purin or the protein content of the diet or the rate of water excretion was varied widely. A final chapter summarizes the monograph. Tables are appended in which are recorded the protocols of the observations which were made. Last of all is an excellent bibliography.

A glance through the bibliography reveals strikingly evidence of how much important work in later years has been done by American biochemists and physiologists on problems of uric acid metabolism. This thesis will be of chief interest to investigators in that particular field.

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COURSE OF POLYCYTHEMIA

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Primary polycythemia is remarkable chiefly for its chronicity and the unusual variations which occur in its course and terminal phases. The disease may be of many years' duration, and the clinical changes may develop so insidiously as to make it impossible to determine the transition from one stage to another, unless this is comprehended, later phases of the condition may appear to be entirely unrelated to the original polycythemic stage.

Any thorough study of the entire course of the disease should include a preliminary consideration of its incipient or developmental phase, which apparently requires several years to reach its peak, although in some instances less time may be required. As no adequate hematologic tests have yet been devised for the diagnosis in this phase, its duration can only be conjectured. And since the blood picture is the diagnostic criterion, it is impossible to determine the presence of the disease until the actual polycythemic stage is reached.

This communication is based on an extensive series of cases of primary polycythemia encountered in hospital and private practice. It represents a study of the clinical and hematologic changes that appear in the subsequent and terminal stages of the disease, such as unusual polynucleosis, leukemia, thrombocythemia, chlorotic polycythemia and rare anemia and their combinations.

The 13 cases presented were selected from a group of 75. In the arranging of their sequence, an endeavor has been made to indicate the variations which may occur during the course of the disease.

ASYMPTOMATIC PHASE

Polycythemia may be asymptomatic. Its presence may be accidentally discovered when the patient appears for a routine examination of the blood or for some unrelated condition. The first 2 cases are examples of this asymptomatic form.

From the Department of Medicine and the Division of Laboratories of the Mount Sinai Hospital

CASE 1—Asymptomatic polycythemia, discovered when the patient was being treated for bleeding of the gums and pyorrhea

I L, a man aged 61, had had no previous illness. He consulted his dentist for construction of a bridge, and it was found necessary to treat the gums for severe pyorrhea. Scraping of the teeth induced marked bleeding. This continued for several days and led the dentist to suspect a hematologic condition.

Examination of the blood revealed the typical changes of polycythemia, viz, hemoglobin, 138 per cent, red blood cells, 10,670,000, platelets, 270,000, white blood cells, 13,600, nonsegmented neutrophils, 13 per cent, segmented neutrophils, 77 per cent, basophils, 1 per cent, lymphocytes, 6 per cent, monocytes, 3 per cent, and volume of red blood cells, 69.7 per cent.

On physical examination a typical polycythemic facies was noted, which the patient's son stated had been present for many years. The spleen was not palpable. The patient had never complained of headaches or dizziness.

CASE 2—Asymptomatic polycythemia, discovered after the patient was rejected for life insurance

A B, a man 45 years of age, had always been in good health. During the latter part of 1935 he applied for life insurance but was rejected because urinalysis showed a heavy trace of albumin. For this reason the patient came to the clinic for observation.

Physical examination revealed a markedly plethoric man, with slightly congested conjunctivas and deep violaceous lips. The heart and lungs were normal. The spleen and liver were not palpable.

Examination of the blood showed hemoglobin, 132 per cent, red blood cells, 7,800,000, platelets, 320,000, white blood cells, 9,600, polymorphonuclears, 80 per cent, eosinophils, 1 per cent, and lymphocytes, 19 per cent.

The urine was amber colored and gave an acid reaction. A heavy trace of albumin was noted but there was no sugar. The specific gravity was 1.012. There were occasional red blood cells and hyaline and granular casts.

The patient was seen at weekly intervals. Subsequent examinations of the blood revealed findings similar to the first ones. The last examination, on April 16, 1936, showed hemoglobin, 133 per cent, red blood cells, 8,410,000, platelets, 320,000, white blood cells, 8,700, nonsegmented neutrophils, 13 per cent, segmented neutrophils, 60 per cent, eosinophils, 4 per cent, neutrophilic myelocytes, 2 per cent, lymphocytes, 19 per cent, monocytes, 2 per cent, and relative volume of red blood cells, 75.75 per cent.

Comment—It is important to note that although this disease presents many symptoms, it may exist despite a feeling of absolute well-being. Were it not for the insurance examination, this patient might never have been seen until years subsequently, when he might have presented unusual anemia or leukemia with splenomegaly.

POLYCYTHEMIC PHASE—SYMPTOMATIC

This is the stage of polycythemia best known to the clinician, i.e., when the clinical and hematologic findings present a clear clinical entity.

During this phase the patient presents such symptoms as headache, dizziness, weakness, paresthesia, a ruddy complexion and redness of the hands and feet. In about 75 per cent of the cases the spleen is enlarged,

the liver is enlarged in about 50 per cent. The blood pressure is often normal, but generally it is moderately elevated, and in some instances there is marked hypertension, the so-called Geisboeck¹ form. The heart may be within normal limits or, more commonly, slightly enlarged to the left, usually coinciding with the blood pressure. On roentgen examination the pulmonary fields as a rule show increased vascular markings. Bleeding from the nose and gums is not infrequent. This is not due to a tendency to bleeding but is the result of congestion of the vascular bed. Vascular occlusion as a frequent complication of this disease has been reported by Oppenheimer.² Moreover, premature death often may result from thrombosis of a vital cerebral vessel. Erythromelalgic symptoms are frequently present when no vascular disturbances are discernible, sometimes these are the sole complaints of the patient. This brief picture is fairly characteristic of the polycythemic or first clinical phase of the disease.

The hemoglobin value and red blood cell count may be overwhelmingly high. The white blood cell count may range from normal to a fairly high level. The differential count in most cases reveals polynucleosis, and the number of eosinophils and basophils may be increased. The red blood cell volume and the total blood volume are always increased.

The duration of the polycythemic phase may be long, possibly ten to twenty years or even longer. Symptomatic and hematologic changes may continue until death, and these may become clarified only when the function of the bone marrow is understood, for primary polycythemia is apparently a disease of the entire bone marrow, not merely of the red blood cell elements. The following is an example of a case of many years' duration.

CASE 3—*Primary polycythemia of long duration*

M. S., a woman 49 years of age (a private patient), was first observed in September 1935.

Symptoms began at the age of 30, with redness of the eyes. Migraine and dizziness, which had previously existed for many years, then became accentuated. Severe backache and pain in the legs supervened and prevented sleep.

At the age of 32 the patient entered Battle Creek (Mich.) Sanitarium under the observation of Dr. Gertrude Johnson,³ who published a report of the case. At that time the complexion was florid, and the liver and spleen were not enlarged. Repeated examinations of the blood showed a red blood cell count ranging between 7,000,000 and 7,500,000. The patient was treated with phlebotomies and

1 Geisboeck, F. Die Bedeutung der Blutdruckmessung für die Praxis, *Deutsches Arch. f. klin. Med.* **83** 362-409, 1905.

2 Oppenheimer, B. S. Vascular Occlusion in Polycythemia Vera, *Tr. A. Am. Physicians* **44** 338-344, 1929.

3 Johnson, G. Polycythemia Vera. Report of Two Cases, *J. A. M. A.* **84** 1253-1254 (April 25) 1925.

benzene, as well as mercury and iodides, although the Wassermann test gave a negative reaction. Roentgen irradiation of the long bones and spleen was given for fifteen days. On leaving the hospital she showed considerable improvement. She felt well for two years, when the symptoms recurred. Four years after her previous admission she re-entered Battle Creek Sanitarium. At that time the findings were essentially the same, treatment was instituted as before, and the patient was discharged somewhat improved.

On Sept 12, 1935, the patient was referred to us by Dr Samuel Silbert. She complained of her original symptoms, which varied from time to time, and, in addition, of severe pain in the finger tips of nine years' duration. For six years, especially during cold weather, there was severe itching over the back and breasts.

The blood count showed hemoglobin, 122 per cent, red blood cells, 7,050,000, platelets, 340,000, white blood cells, 14,500, nonsegmented neutrophils, 18 per cent, segmented neutrophils, 52 per cent, eosinophils, 3 per cent, lymphocytes, 23 per cent, monocytes, 4 per cent, and relative volume of red blood cells, 52.5 per cent.

The spleen was not palpable. The patient was treated with acetylphenylhydrazine and small phlebotomies. The pain in the finger tips and the itching subsided. When she was last seen there was considerable improvement.

Comment—This case is unusual because of the number of years during which the polycythemic stage continued. Eventually, barring accidents, this patient may show a condition similar to that presented in one of the following cases.

POLYCYTHEMIA ASSOCIATED WITH THROMBOCYTHEMIA

In about 30 per cent of the cases the number of blood platelets was increased.⁴ In such cases thrombosis is more prone to develop. This fact is not surprising, as a potent clotting factor is superimposed on an already slowly circulating viscid blood.

CASE 4—*Polycythemia associated with thrombocythemia*

S. S., a man 69 years of age, a tailor, was admitted to the service of Dr George Baehr on Oct 29, 1934, complaining of chronic productive cough and increasing dyspnea of ten years' duration. Five and one-half years previously, severe intestinal hemorrhages without pain or cramps developed, and the patient was admitted to another hospital. The hemorrhages were profuse for three days, and severe anemia ensued. After a blood transfusion there was considerable improvement. Gastrointestinal studies at that time revealed no lesion. Three weeks before admission to the clinic he had another severe intestinal hemorrhage, but his condition improved without a transfusion.

Physical examination revealed a thin elderly man with a characteristic florid facial appearance. The spleen was felt 1 fingerbreadth below the costal margin. The liver was not palpable.

⁴ The blood platelets were enumerated according to the method of Ottenberg and Rosenthal (Ottenberg, R., and Rosenthal, N. A New and Simple Method for Counting Blood Platelets, *J. A. M. A.* 69:999 [Sept 22] 1917), sodium citrate (3 per cent) being used. The normal range varies from 200,000 to 300,000. A diagnosis of thrombocytosis or thrombocythemia was considered if the number of platelets exceeded 500,000 per cubic millimeter.

The blood count on May 18, 1934, showed hemoglobin, 100 per cent, red blood cells, 8,100,000, platelets, 1,500,000, white blood cells, 24,000, nonsegmented neutrophils, 7 per cent, segmented neutrophils, 68 per cent, eosinophils, 1 per cent, basophils, 2 per cent, lymphocytes, 21 per cent, monocytes, 1 per cent, total blood volume, 6,250 cc (120 cc per kilogram), and volume of red blood cells, 60 per cent

Comment—This patient was not observed until many years after the development of polycythemia. This was associated with marked thrombocythemia, which probably resulted in thrombosis of a mesenteric vein and intestinal hemorrhage. From observation of other patients it is concluded that such complications are more likely to occur in cases of this type.

POLYCYTHEMIA ASSOCIATED WITH INCREASED LEUKOBLASTIC ACTIVITY OR LEUKOBLASTIC AND MEGAKARYOCYTIC ACTIVITY

The number of white blood cells is frequently increased in the peripheral blood, and, as has been pointed out by di Guglielmo,⁵ the thrombocytes may be present in large numbers. Individual cases vary in this respect. The polycythemic phase may be accompanied by leukocythemia or thrombocythemia or both. Any and all combinations are possible, and when it is realized that exhaustion of one element may occur while another begins or continues to hyperfunction, one can more readily understand the wide variation in the hematologic pictures presented during the slow progress of this disease. Increased leukoblastic and often megakaryocytic activity associated with polycythemia is well illustrated by the following cases.

CASE 5—*Polycythemia associated with polynucleosis (polynuclear cell leukemia)*

S. N., a man 52 years of age, was admitted to the service of Dr. B. S. Oppenheimer on Oct. 20, 1935. Twenty years previously, after extraction of a tooth, the patient first noted a tendency to bleeding, which continued more than a day. Eighteen years previously he consulted a physician because of heart burn and belching. At that time the spleen was enlarged, and attention was directed to clubbing of the fingers. About twelve years previously left hemiplegia developed, and the patient was removed to Beth Israel Hospital, where the condition was diagnosed as primary polycythemia.

The blood count at that time showed hemoglobin, 133 per cent, red blood cells, 11,000,000, white blood cells, 32,800, nonsegmented neutrophils, 16 per cent, segmented neutrophils, 80 per cent, and lymphocytes, 4 per cent.

Treatment consisted of phenylhydrazine, phlebotomies and irradiation.

On November 25 the patient was admitted to Mount Sinai Hospital, complaining of large, tarry stools and the vomiting of blackish material. The presence of a bleeding gastric ulcer was suspected, but his condition did not warrant roentgen examination.

⁵ di Guglielmo, G. Eritroleucemia e piastrinemia, *Folia med.* 6 1, 36, 55, 81 and 101, 1920.

The blood count showed hemoglobin, 100 per cent, red blood cells, 7,350,000, platelets, 280,000, white blood cells, 59,000, nonsegmented neutrophils, 20 per cent, segmented neutrophils, 70 per cent, basophils, 3 per cent, and myelocytes, 7 per cent

The patient declined steadily, in spite of many transfusions, and died five days after entry

Comment—This case is an example of the long course of polycythemia, which probably had existed for eighteen years. During the latter part of the polycythemic phase there was evidence of leukocytic activity, as manifested by the presence of large numbers of mature and immature neutrophils. In addition, a severe complication of this disease was present, viz, gastric ulcer. Duodenal or gastric ulcer is found in about 10 per cent of these cases. Although it is unusual for such ulcers to bleed, when bleeding does occur it is difficult to control, as is well illustrated in this case. Bleeding of any kind, either spontaneous or postoperative, is always an alarming symptom in this condition.

CASE 6—*Polycythemia and myeloid leukemia (erythroleukemia)*

H R, a man 75 years of age, was admitted to the service of Dr B S Oppenheimer on July 3, 1934, complaining of dyspnea, anorexia and pain in the left upper quadrant of the abdomen of two years' duration.

Physical examination revealed an old man of highly plethoric appearance. The inguinal nodes were palpable bilaterally. The liver was felt 4 fingerbreadths below the costal margin. The spleen extended to the umbilicus.

The blood count showed hemoglobin, 135 per cent, red blood cells, 9,500,000, platelets, 160,000, white blood cells, 189,000, nonsegmented neutrophils, 32 per cent, segmented neutrophils, 40 per cent, eosinophils, 1 per cent, lymphocytes, 2 per cent, myelocytes, 25 per cent, normoblasts, 6 per hundred white blood cells, and blood volume, 215 cc per kilogram.

The patient was given roentgen treatment to the spleen and femurs and was phlebotomized but declined rapidly and died three weeks after admission to the hospital. Postmortem examination was refused.

Comment—This case is typical of erythroleukemia, in which both active erythroblastic and leukoblastic involvement of the bone marrow are present. It has been suggested that treatment is responsible for the development of leukemia in cases of polycythemia. To our knowledge this man had not received any therapy prior to admission to the hospital. Others might be of the opinion that the polycythemia followed or was associated with the leukemia. Such a case has been reported by Ghiron,⁶ but one has never been observed by us.

CASE 7—*Polycythemia associated with leukocytosis, polynucleosis (so-called polynuclear cell leukemia) and thrombocythemia*

E S, a woman 60 years of age, was admitted to the service of Dr Leo Kessel on Oct 16, 1929, with a history of epigastric burning, pain in the lower end of

6 Ghiron, M. Considerazioni sopra un case di eritro-leucemia, *Haematologica* 3 162-172, 1922.

the sternum and pain in the lumbosacral region. There were slight dyspnea on exertion and swelling of the legs.

Physical examination revealed a plethoric complexion and polycythemic mucous membranes. There were some thyroid enlargement and cervical and axillary adenopathy. The heart was slightly enlarged to the left. The liver and spleen were likewise enlarged.

The blood count showed hemoglobin, 130 per cent, red blood cells, 8,300,000, platelets, 456,000, white blood cells, 19,900, polymorphonuclears, 91 per cent, eosinophils, 3 per cent, lymphocytes, 4 per cent, and monocytes, 2 per cent.

The patient was seen again five years later, complaining of similar symptoms. By that time the abdomen had become considerably enlarged, as had also the heart, liver and spleen. There were free fluid in the abdominal cavity and marked edema of the lower extremities.

The blood count showed hemoglobin, 85 per cent, red blood cells, 5,320,000, platelets, 840,000, white blood cells, 40,000, nonsegmented neutrophils, 13 per cent, segmented neutrophils, 82 per cent, eosinophils, 1 per cent, lymphocytes, 1 per cent, and monocytes, 3 per cent.

The patient steadily declined and died two weeks after admission to the hospital. Postmortem examination revealed dark red bone marrow. Microscopically there was an enormous increase in megakaryocytes.

Comment—In this case all the myeloid elements were increased. Toward the end, although the red blood cell count was at a much lower level, the number of white blood cells and platelets was greatly increased. The differential count showed striking polynucleosis. We have observed the development of true leukemia after the polynuclear phase.

CASE 8—*Polycythemia associated with myeloid leukemia and thrombocythemia*

P. H., a Negress 39 years of age, was admitted to the service of Dr. B. S. Oppenheimer on Jan. 18, 1936. About five years previously the patient suffered right hemiplegia. Four years previously the menses suddenly ceased. For two years there had been dyspnea on exertion, with moderate edema of the ankles at night. Ten months previously the abdomen gradually became enlarged, and profuse night sweats and loss of weight occurred.

Physical examination revealed a puffy-faced dyspneic Negress with mild exophthalmos. A hard, calcified nodule was present in the thyroid gland. There were small, hard, discrete nodes in the cervical, supraclavicular and inguinal regions. There was dullness over the upper lobe of the right lung, with rales over the apex. The heart was enlarged to the left. The spleen extended to the umbilicus and the liver to the crest of the ilium. There was edema of both lower extremities.

The blood count showed hemoglobin, 102 per cent, red blood cells, 6,000,000, platelets, 640,000, white blood cells, 60,000, nonsegmented neutrophils, 6 per cent, segmented neutrophils, 88 per cent, eosinophils, 2 per cent, basophils, 1 per cent, neutrophilic myelocytes, 2 per cent, myeloblasts, 1 per cent, reticulocytes, 5 per cent, total blood volume, 8,185 cc (141 cc per kilogram), and relative cell volume, 53 per cent.

Sternal biopsy showed the presence of many megakaryocytes. The patient died at home two weeks after discharge from the hospital.

Comment—This case probably represents a more advanced stage of the condition presented in the preceding case (case 7) and corresponds with di Guglielmo's⁵ erythroleukothrombocythemia. The pic-

ture is similar save that the white blood cells began to show true leukemic changes

CHLOROTIC POLYCYTHEMIA

A patient with primary polycythemia may respond to therapy, and a normal blood picture may be obtained after a varying period. However, there is a tendency for the hemoglobin value and red blood cell count to return to their previous high levels. We have observed that after prolonged treatment, particularly with phlebotomies and acetylphenylhydrazine, the hemoglobin value tends to remain normal or subnormal while the red blood cell count returns to its former high mark. Although we believe that most phases may occur spontaneously, we incline to the opinion that the so-called chlorotic stage is directly due to therapy. The disproportion between the red blood cell count and the hemoglobin value in such cases may be extreme, and the red blood cells when examined in stained smears resemble those seen in severe hypochromic anemia. On rare occasions the response to treatment might result in hyperchromic anemia.

CASE 9—*Chlorotic polycythemia*

I P, a man 39 years of age, was admitted to the hematologic clinic of the Mount Sinai Hospital in March 1933 with a history of cramps in the upper portion of the abdomen seven years prior to entry. A gastrointestinal roentgen study was made at this time and revealed a duodenal ulcer. In addition to the gastric disorder, the patient suffered considerably from headache and vertigo, but little significance had been attached to this until a few months before entry, when it was noted that the spleen was enlarged and the color unusually good.

Examination of the blood revealed findings typical of polycythemia. Treatment was instituted with acetylphenylhydrazine, which induced marked anemia, from which recovery was gradual. After polycythemia recurred, roentgen therapy was given and the patient was phlebotomized at frequent intervals during this treatment.

The blood count before treatment showed hemoglobin, 128 per cent, red blood cells, 9,250,000, platelets, 280,000, white blood cells, 20,000, nonsegmented neutrophils, 6 per cent, segmented neutrophils, 70 per cent, eosinophils, 3 per cent, basophils, 2 per cent, lymphocytes, 17 per cent, and monocytes, 2 per cent.

About three months subsequently hematuria occurred, with pain across the back. The uric acid content of the blood was found to be increased (7 mg per hundred cubic centimeters). A calculus was suspected. This was confirmed by cystoscopy.

The blood count made one year after the first examination showed hemoglobin, 80 per cent, red blood cells, 8,000,000, platelets, 350,000, white blood cells, 14,500, nonsegmented neutrophils, 5 per cent, segmented neutrophils, 85 per cent, eosinophils, 2 per cent, basophils, 1 per cent, and lymphocytes, 7 per cent.

The blood count made one year subsequently showed hemoglobin, 84 per cent, red blood cells, 10,200,000, and platelets, 600,000.

POLYCYTHEMIA WITH A LONG NORMAL STATE

The response to therapy in this disease varies markedly in different patients. A normal clinical and hematologic state may usually be induced by treatment with acetylphenylhydrazine, irradiation or phlebotomies, singly or in combination. The duration of the induced, so-called normal

phase varies greatly. It has been our experience that one or two courses of roentgenotherapy are most satisfactory in maintaining a long normal state.

CASE 10—*Polycythemia with a long normal state*

L. F., a man 49 years of age, was admitted to the service of Dr. George Baehr on Oct. 10, 1928, complaining of dizzy spells which began two years prior to entry. Six months previously severe intermittent pain developed in the right big toe, which became red and swollen. The patient stated that his complexion had been florid for many years.

Physical examination revealed a highly plethoric type of person. The heart and lungs were normal. The spleen and liver were enlarged.

The blood count showed hemoglobin, 135 per cent, red blood cells, 13,800,000, platelets, 560,000, white blood cells, 9,400, nonsegmented neutrophils, 1 per cent, segmented neutrophils, 77 per cent, lymphocytes, 16 per cent, monocytes, 6 per cent, blood volume, 168 cc. per kilogram, and relative cell volume, 64.6 per cent.

This patient was treated with phenylhydrazine, phlebotomies and irradiation, but the condition was poorly controlled until a complete course of irradiation had been given, when the blood count became normal.

The blood count on Nov. 27, 1931, showed hemoglobin, 92 per cent, and red blood cells, 5,500,000.

Meanwhile, no therapy was given.

The blood count on March 1, 1934, showed hemoglobin, 93 per cent, red blood cells, 5,000,000, platelets, 240,000, white blood cells, 8,000, nonsegmented neutrophils, 2 per cent, segmented neutrophils, 58 per cent, basophils, 2 per cent, and lymphocytes, 38 per cent.

The blood count remained normal until January 1935, when the hemoglobin value rose to 114 per cent and the red blood cell count to 7,250,000. The patient was given a course of roentgen treatment. Afterward the blood picture became normal and has since remained normal in every respect.

ANEMIC PHASE

It may be generally stated that unless the disease is terminated early in its course by a vascular complication or later by the development of the erythroleukemic phase, the tendency is ultimately toward marked anemia. Patients who reach this stage may be regarded as having survived the entire course of the disease.

The anemic phase varies in different patients. In this stage all the elements may be depressed, so that, in addition to the anemia, there are leukopenia and thrombopenia. However, the platelets may persist in large numbers, and anemia may then be associated with thrombocythemia. On the other hand, the leukocytes may increase in number, while the erythropoietic activity is depressed, and the patient, if seen for the first time, will appear to present evidence of myeloid leukemia.

The following cases illustrate these variations.

CASE 11—*Early spent phase, with slight leukemic changes*

G. R., a married woman 66 years of age, first attended the hematologic clinic in 1927, with a history of having had blood-shot eyes and a peculiar disturbance

in vision, when everything seemed to tremble, frequently dizzy spells associated with nausea but no headache, and pain in the abdomen and legs

Physical examination revealed a woman of florid appearance. The heart and lungs were essentially normal. The blood pressure was moderately elevated. The spleen was palpable.

The blood count at this time showed hemoglobin, 155 per cent, red blood cells, 12,200,000, platelets, 260,000, white blood cells, 18,000, polymorphonuclears, 80 per cent, eosinophils, 3 per cent, lymphocytes, 12 per cent, neutrophilic myelocytes, 4 per cent, and myeloblasts, 1 per cent.

The patient was given roentgen therapy to the long bones and phenylhydrazine. The blood count was fairly well controlled. In the past three years it has remained rather low, with little or no therapy.

The blood count in 1935 showed hemoglobin, 79 per cent, red blood cells, 5,040,000, platelets, 170,000, white blood cells, 19,200, nonsegmented neutrophils, 16 per cent, segmented neutrophils, 62 per cent, eosinophils, 1 per cent, basophils, 2 per cent, neutrophilic myelocytes, 8 per cent, lymphocytes, 7 per cent, and monocytes, 4 per cent.

Subsequent counts up to the present have been similar. Now no therapy is being given. The patient has no complaints but still retains a moderately polycythemic appearance.

Comment—This case is reported to direct attention to the normal phase, in which there is relatively slight anemia. The patient has remained in this state for three years without treatment. The persistence of the myelocytes is possibly a forerunner of the leukemic phase, which may become more marked as the anemia progresses.

CASE 12—*Spent polycythemia with leukemic changes*

M. W., a woman 46 years of age, was admitted to the service of Dr. George Baehr on July 10, 1934, with a history of vertigo and headaches, which began seventeen years previously. Shortly after their onset the condition was diagnosed as primary polycythemia. At that time the red blood cell count was 11,000,000.

The patient was given benzene and roentgen therapy for thirteen years, during which the symptoms were well controlled. Treatment was then stopped because it seemed no longer indicated. One year later episodes of chills and fever developed, the cause being unknown. Between these episodes the patient felt perfectly well except for slight weakness. The complaints on entry were of vertigo, headache, chills and fever.

Physical examination on the last entry revealed a pale, fairly well nourished woman who appeared chronically ill. The heart and lungs were normal. The spleen was hard and was palpable 3 fingerbreadths below the costal margin.

The blood count showed hemoglobin, 69 per cent, red blood cells, 3,560,000, platelets, 90,000, white blood cells, 10,400, nonsegmented neutrophils, 10 per cent, segmented neutrophils, 50 per cent, eosinophils, 2 per cent, basophils, 1 per cent, lymphocytes, 29 per cent, monocytes, 2 per cent, neutrophilic myelocytes, 1 per cent, myeloblasts, 5 per cent, and normoblasts, 2 per hundred white blood cells.

Nothing was found to account for the chills. Although quinine prevented the attacks, so also did acetylsalicylic acid when taken in moderate doses. The patient was observed by us for about two years. Numerous transfusions as well

as injections of liver extract were given without much effect. During the last year of our observation it was noted that at the site of each injection, peculiar noninflammatory swellings appeared. Biopsy of the bone marrow revealed osteosclerosis and some areas of active hemopoiesis. A few months subsequently a large tumor appeared at the site of the sternal biopsy. The patient died eventually at Montefiore Hospital.

Postmortem examination revealed that the leukopoiesis had, since the biopsy, become hyperactive, with resulting large tumor-like masses, both medullary and extramedullary, which were found to be leukosarcomatous. The femoral marrow was the site of active myeloid hyperplasia.

Comment—This case is of particular interest as the disease followed its complete course, passing through its various phases, viz the polycythemic, the normal and the anemic or spent phase with osteosclerosis and finally leukosarcomatosis. The changes from one phase to another could be identified to some extent. A case of this character if the patient is observed for the first time during a late phase may present a puzzling diagnostic problem.

CASE 13—*Spent polycythemia with thrombocythemia*

J. G., a man 62 years of age, was admitted to the service of Dr. B. S. Oppenheimer on Jan. 9, 1930, with an essentially unimportant history. Eighteen months before entry, painful swelling of the right foot developed. A year prior to entry the patient suddenly became weak and dizzy and had to be carried home, and since then had never felt well, weakness and marked loss of weight being the chief complaints. He was finally admitted to the hospital because of severe anemia, progressive weakness and pallor. Prior to this illness the complexion was particularly ruddy.

Physical examination revealed a pale, poorly nourished man. The mucous membranes were pale. The lungs were clear. The heart was slightly enlarged to the left. The spleen was hard and extended 3 fingerbreadths below the costal margin. The liver extended down to about the same level.

The blood count showed hemoglobin, 47 per cent, red blood cells, 3,200,000, platelets, 2,200,000, white blood cells, 21,400, nonsegmented neutrophils, 6 per cent, segmented neutrophils, 67 per cent, eosinophils, 5 per cent, basophils, 5 per cent, lymphocytes, 9 per cent, monocytes, 5 per cent, neutrophilic myelocytes, 1 per cent, and basophilic myelocytes, 2 per cent.

Biopsy of bone marrow revealed active leukopoiesis and a conspicuous increase in the megakaryocytes.

Because of the great increase in the platelet count (which was always in excess of 1,000,000 and at times over 2,000,000), the condition was suggestive of thrombosis of the splenic artery. However, because of the history of a ruddy complexion, the biopsy report of the bone marrow and the differential count, the most logical diagnosis was primary polycythemia in its spent phase.

Subsequent studies of the blood revealed similar pictures. The patient became too weak to attend the clinic and died about two years after entry to the hospital.

Comment—This case is an example of spent polycythemia in the sense that the erythropoietic elements were lacking in the general circulation and somewhat depressed in the bone marrow. The megakaryo-

cytic and leukocytic elements became more active as the erythropoietic elements became exhausted. Although the patient was not seen during the polycythemic phase, the diagnosis of polycythemia was made probable by the finding of thrombocythemia and, to some extent, by the previous asymptomatic history of polycythemia.

COMMENT

Primary polycythemia is always characterized at the beginning by erythropoietic activity, which may persist for many years. However, this activity eventually declines or may be supplemented at any time by unusual leukoblastic or megakaryocytic activity, producing the various hematologic and clinical pictures just described.

This disease, therefore, should be considered as an ever changing condition, its various transitions being so gradual as to be almost imperceptible. The classification into phases has been arbitrary, and it may be noted that there are no sharp demarcating lines.

As the majority of patients seen at the onset of the condition receive treatment, a normal state of the blood may be produced. In the early active years of the disease the tendency is invariably for the polycythemic state to return, and occasionally a peculiar blood picture may develop, that of so-called chlorotic polycythemia. In such a phase the hemoglobin value remains fixed at a low level (80 per cent or less), while the red blood cell count ranges from 7,000,000 to 10,000,000. In such cases early leukemic changes may appear at the same time. Patients who have been under treatment may of course show leukemia while true polycythemia exists. Only careful and continued observation in these cases for many years will enable one to comprehend the slow development of the various phases of the disease as a result of the activities or exhaustion of certain elements in the bone marrow.

It is obvious from a review of the literature on primary polycythemia that little attention has been directed to the peculiar and intricate course of this disease. Although first described by Vaquez,⁷ in 1892, the condition was not definitely accepted as a disease entity until several years subsequently.

Osler⁸ in 1903, reported 4 cases and reviewed those cited in the literature. In this report he stated: "Future investigators will determine whether we have here in reality a new disease. The clinical picture is certainly very distinctive, the symptoms, however, are some-

⁷ Vaquez, H. Sur une forme speciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante, *Bull. med.*, Paris **6** 849, 1892.

⁸ Osler, W. Chronic Cyanosis with Polycythemia and Enlarged Spleen. A New Clinical Entity, *Am. J. M. Sc.* **126** 187-201, 1903.

what indefinite and the pathology quite obscure" He pointed out that the clinical picture is striking, but because of the fact that the long duration of the disease with its many hematologic and clinical variations was then unknown, the picture was also incomplete

A broader conception was given in 1905 in reports by Weber⁹ and Blumenthal¹⁰ They attempted to show that polycythemia is associated with hyperactivity of the white blood cell elements in the bone marrow, which may or may not be reflected in the peripheral blood In the case reported by Weber, the white blood cell count was normal, and at times there was leukopenia His contention was based on a study of bone marrow made in a case reported with Watson,¹¹ in which he suggested "The changes were, however, not exclusively of an erythroblastic kind and it may be doubted whether the erythrocytic producing function of the bone marrow can ever be greatly increased without the myelocytes being to some extent involved in the activity"

In the case reported by Blumenthal,¹⁰ the blood picture was typical of both polycythemia and leukemia He termed the condition myelogenic polycythemia At postmortem examination the bone marrow appeared to be typical of that in leukemia Hitherto such a case had not been described, and as a result there was much speculation as to the relation of leukemia and polycythemia The important fact to note, however, is that the original concept of the scope of the disease had now been broadened But it was not until many years subsequently that this was further amplified by a description of a case during the anemic phase

Freund,¹² in 1919, noted the transition of established polycythemia of many years' duration to hyperchromatic anemia resembling pernicious anemia Three additional cases of severe anemia following polycythemia were reported by Minot and Buckman¹³ In all their cases considerable enlargement of the spleen was observed during the development of the anemic phase In 1 of these cases six years elapsed from the onset of the anemic phase until death In 1928, 2 similar

9 Weber, F P A Case of Splenomegalic or Myelopathic Polycythemia with True Plethora and Arterial Hypertension, Without Cyanosis, *Lancet* **1** 1254-1260, 1905

10 Blumenthal, R Un case de polycythémie myélogène, *Bull Acad roy de med de Belgique* **19** 775-818, 1905

11 Weber, F P, and Watson, J H A Case of Chronic Polycythemia with Enlarged Spleen, Probably a Disease of the Bone Marrow, *Tr Clin Soc London* **37** 115-135, 1903-1904

12 Freund, H Polyzythämie mit Ausgang in perniziöse Anämie, *München med Wchnschr* **66** 84, 1919

13 Minot, G, and Buckman, T E Erythremia (Polycythemia Rubra Vera), *Am J M Sc* **166** 469-489, 1923

cases were reported by Delhougne, Gotschlich and Froboese,¹⁴ and later another was reported by Avery¹⁵

The cause of this anemic phase of the disease is not clearly understood. According to Minot and Buckman¹³ it is produced by leukopoietic activity, with resulting depression of the erythropoietic elements. Avery¹⁵ stated that there is a possibility of acceleration of the hemolytic factor. In the case reported by him some evidence of increased hemolysis was revealed by the van den Bergh reactions and by the increased excretion of urobilin in the stool. Increased deposits of hemosiderin in the liver also indicated excessive hemolysis.

In 3 patients observed by us during the anemic phase, biopsy of the bone marrow was made. This showed marked leukopoietic and megakaryocytic activity in 1 case (case 13), corresponding with the observation of Minot and Buckman¹³. In 2 other cases (case 12 and another not reported in this series) biopsy of the sternal bone marrow revealed extensive osteosclerosis, as recently reported by Hirsch.¹⁶ However, it is possible that certain parts may remain active and may show a neoplastic tendency (myelosarcomatosis, as in case 12) in the terminal state.

The relation of the megakaryocytes and the blood platelets to polycythemia has become an important consideration since Hutchison and Miller,¹⁷ Askanazy¹⁸ and others noted a marked increase in the megakaryocytes in the bone marrow and di Guglielmo⁵ found veritable thrombocythemia in some cases of polycythemia. Similar cases have since been reported, notably by Weber¹⁹ and Bach.²⁰ Luedeke²¹ and Parenti²² have likewise called attention to the widespread thromboses

14 Delhougne, F., Gotschlich, E., and Froboese. Ueber Polyzzythämie mit Ausgang in Anämie, *Deutsches Arch f klin Med* **160** 257-266, 1928

15 Avery, H. A Pernicious Type of Anemia Following Erythremia, *Lancet* **1** 342-344, 1930

16 Hirsch, E. F. Generalized Osteosclerosis with Chronic Polycythemia, *Arch Path* **19** 91-97 (Jan.) 1935

17 Hutchison, R., and Miller, C. H. A Case of Splenomegalic Polycythaemia, with Report of Post-Mortem Examination, *Lancet* **1** 744-746, 1906

18 Askanazy, M. Knochenmark, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1927, vol. 1, p. 2

19 Weber, F. P. Erythraemia with Migraine, Gout and Intracardiac Thrombosis, *Lancet* **2** 808-809, 1934

20 Bach, K. Ueber Thrombosebereitschaft bei Polycythaemie vera, *Inaug Dissert*, University of Leipzig, 1934

21 Luedeke, H. Thrombophilie und Polycythaemie, *Virchows Arch f path Anat* **293** 218-252, 1934

22 Parenti, G. C. Policitemia vera (M di Vaquez) con diatesi tromboplastica, *Riv di clin med* **36** 287-310, 1935

in certain cases of this type, designated as thrombophilia. This particular aspect may be present in all phases of polycythemia, including the leukemic or anemic stage (as in case 13 of this group). The recognition of all phases of polycythemia is of great practical importance.

SUMMARY

Primary polycythemia is a disease of long duration. Occasionally the early stage may be asymptomatic, but usually it is symptomatic.

After a period of years one or more of a variety of clinical conditions apparently develop, as a result either of the hyperactivity of the leukopoietic and megakaryocytic systems or of exhaustion of the erythropoietic system.

In its terminal stages this disease may become leukemic, thrombocytic or anemic or may reveal various remarkable combinations of any or all of these phases.

UTILIZATION OF INTRAVENOUSLY INJECTED SODIUM *d*-LACTATE AS A TEST OF HEPATIC FUNCTION

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In previous papers we¹ reported on the utilization of sodium *d*-lactate when injected intravenously into normal persons and into patients with acute diffuse hepatic parenchymal injury. As a result of these observations we suggested that the utilization of this substance be employed as a test of hepatic function in the differentiation between jaundice due to extrahepatic obstruction and jaundice due to hepatic damage²

In the present paper we are reporting on further studies of the utilization of sodium *d*-lactate as a test for the differentiation of these two forms of jaundice

The rationale for the use of sodium *d*-lactate was described in the previous reports¹. The test is dependent essentially on the ability of the intact parenchyma of the liver to convert into glycogen the lactic acid that is circulating in the blood stream. It should again be emphasized that the metabolism of *d*-lactate is quite different from that of the racemic or the *l*-salt, with which all previous clinical work has been done, *d*-lactic acid is a physiologic substance which plays a definite role in the intermediary phases of carbohydrate metabolism. Thus, Meyer-

From the Medical Service of Dr. George Baehr and the Division of Laboratories of the Mount Sinai Hospital

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1 Soffer, L. J., Dantes, D. A., Newburger, R., and Sobotka, H. (a) Metabolism of Sodium *d*-Lactate. I Utilization of Intravenously Injected Sodium *d*-Lactate by Normal Persons, *Arch. Int. Med.* **60**: 876 (Nov.) 1937, (b) II Utilization of Intravenously Injected Sodium *d*-Lactate by Patients with Acute Diffuse Parenchymal Injury of the Liver, *ibid.* **60**: 882 (Nov.) 1937

2 Soffer, L. J., Dantes, D. A., and Sobotka, H. Sodium *d*-Lactate Blood Clearance as a Test of Liver Function, *Proc. Soc. Exper. Biol. & Med.* **36**: 692, 1937

hof and Lohmann³ found that isolated hepatic tissue of the rat was able to synthesize carbohydrate from *d*-lactic acid but hardly from the *l*-lactic acid. Cori and Cori⁴ have pointed out that if 95 mg per hundred grams of body weight of *d*-lactic acid per hour is injected into rats, there occurs no appreciable increase in the lactic acid content of either the blood or the urine, while if the experiments are repeated with sodium *dl*-lactate, a considerable urinary excretion of lactic acid occurs. These authors found that from 40 to 95 per cent of the sodium *d*-lactate given orally or injected subcutaneously is retained as glycogen in the liver and that none is excreted in the urine. In contrast to this, they found that 30 per cent of the *l*-lactic acid is excreted in the urine and that hardly any glycogen is formed in the liver. Himwich, Koskoff and Nahum,⁵ working with decerebrate dogs, found that the main site of formation of lactic acid was the muscle, while the liver was chiefly concerned with its removal from the blood stream and its conversion into glycogen. This agrees with the conclusion stated by Cori and Cori,⁶ that injections of epinephrine which cause a disappearance of glycogen from the muscle in normal rats lead to the formation of glycogen from lactic acid in the liver. Abramson, Eggleton and Eggleton,⁷ working with racemic sodium lactate, found that in the anesthetized dog neither the muscles nor the liver synthesizes glycogen or dextrose from the racemate.

METHOD

With the patient at rest in bed, 75 mg per kilogram of body weight of 12 to 14 per cent solution of sodium *d*-lactate was injected intravenously during fasting. A control sample of blood (5 cc) was collected before the injection and another specimen thirty minutes after the injection. The specimens were collected under sodium fluoride. Lactic acid determinations were obtained by

3 Meyerhof, O, and Lohmann, K. Ueber den Unterschied von *d*- und *l*-Milchsäure für Atmung und Kohlehydratsynthese im Organismus, *Biochem Ztschr* **171**:421, 1926.

4 Cori, C F, and Cori, G T. Glycogen Formation in the Liver from *d*- and *l*-Lactic Acid, *J Biol Chem* **81**: 389, 1929.

5 Himwich, H E, Koskoff, Y D, and Nahum, L H. Changes in Lactic Acid and Glucose in the Blood on Passage Through Organs, *Proc Soc Exper Biol & Med* **25**: 347, 1928.

6 Cori, C F, and Cori, G T. Mechanism of Epinephrine Action. Influence of Epinephrine on Carbohydrate Metabolism of Fasting Rats, with Note on New Formation of Carbohydrates, *J Biol Chem* **79**: 309, 1928.

7 Abramson, H A, and Eggleton, P. Utilization of Intravenous Sodium *d*-Lactate. I. Excretion by the Kidneys and Intestines, *J Biol Chem* **75**: 745, 1927, II. Changes in the Acid-Base Equilibrium as Evidence of Utilization, *ibid* **75**: 753, 1927. Abramson, H A, Eggleton, G M, and Eggleton, P. III. Glycogen Synthesis by the Liver, Blood Sugar, Oxygen Consumption, *ibid* **75**: 763, 1927.

the method of Friedemann and his colleagues,⁸ all being obtained in duplicate. No untoward reaction was observed in any of the patients after the injection of sodium *d*-lactate.

RESULTS

We are presenting the results obtained in 76 instances in which this test was employed.

The normal person is capable of utilizing all or almost all the injected *d*-lactate within thirty minutes.^{1a} In a number of instances the lactic acid content of the blood fell below the control level within this period. We regard as abnormal the retention of 5 mg or more per hundred cubic centimeters of the injected lactate above the control value at the end of one-half hour.⁹

In table 1 are presented the data obtained for 25 normal persons. These were patients who had had an uncomplicated herniotomy, appendectomy or hemorrhoidectomy. The test was performed within five to eight days after operation, just before the patient's dismissal from the hospital. None of this group showed a retention of 5 mg or more per hundred cubic centimeters of the injected lactate at the end of one-half hour.

TABLE 1—*Normal Conditions*

Number of Cases	Lactic Acid Retention After 30 Minutes, Mg per 100 Cc
9	0
2	0.1 to 0.9
3	1.0 to 1.9
5	2.0 to 2.9
3	3.0 to 3.9
1	4.0 to 4.9
0	5.0 and over

In table 2 are recorded the data for 27 patients with acute diffuse hepatic parenchymal damage with jaundice. These patients had catarrhal and arsphenamine icterus and showed a typical clinical course, with recovery in all instances. Twenty-six of these 27 patients showed retention of 5 mg or more per hundred cubic centimeters of the injected sodium *d*-lactate after thirty minutes. In contrast to this group, table 3 shows the results obtained in 13 instances of jaundice due to extra-hepatic obstruction. The diagnosis was confirmed in each instance either by operation or by necropsy. Of this group of 13 patients, only 1 (case 5) showed an abnormal retention of sodium *d*-lactate. This patient, however, had considerable fever before the operation, and a section of liver removed for biopsy at operation showed severe cholangitis, with associated damage of the parenchymal cells.

⁸ Friedemann, T. E., Cotonio, M., and Shaffer, P. A. Determination of Lactic Acid, *J Biol Chem* **73** 335, 1927. Friedemann, T. E., and Kendall, A. I. Determination of Lactic Acid, *ibid* **82** 23, 1929.

⁹ Soffer, Dantes, Newburger and Sobotka.^{1b} Soffer, Dantes and Sobotka.²

TABLE 2—Hepatitis

Case No	Lactic Acid Retention After 30 Min, Mg per 100 Cc	Ratio of Total Cholesterol to Cholesterol Ester	Excretion of Hippuric Acid (Sodium Benzoate Test), Gm in 4 Hr	Excretion of Galactose, Gm in 5 Hr	Excretion of Urobilin	Diagnosis
1	10.8	300/115	0.66	4.33		Catarrhal jaundice
2	9.4	220/45	2.05	3.88		Catarrhal jaundice
3	9.9	325/87	0.95	1.85		Catarrhal jaundice
4	5.0	290/95	1.02	2.08		Catarrhal jaundice
5	9.6	260/120	1.18	1.50		Catarrhal jaundice
6	6.8	190/30	4.05	0.60		Catarrhal jaundice
7	26.1	180/55	0.53	5.50		Catarrhal jaundice
8	12.2	280/180	2.00	2.40		Catarrhal jaundice
9	6.3	210/35	0.96	5.40		Catarrhal jaundice
10	8.3	125/trace	0.99	5.50		Catarrhal jaundice
11	10.0	165/65	1.42	6.10		Catarrhal jaundice
12	17.6	210/35	3.10	2.73		Catarrhal jaundice
13	9.5	250/80		2.55	1.40	Catarrhal jaundice
14	7.2		1.10	9.80	1.10	Catarrhal jaundice
15	4.3	470/230	0.76	0.93	1.160	Sclerotic jaundice
16	10.4	575/270	2.30	0	1.10	Catarrhal jaundice
17	6.2	440/115	2.40	5.84		Catarrhal jaundice
18	10.8	260/55		0	1.160	Catarrhal jaundice
19	8.8	170/trace	0.26	5.00	1.20	Catarrhal jaundice
20	5.4					Catarrhal jaundice
21	7.5	250/96	1.50	9.49	1.320	Arsphenamine jaundice
22	7.2	460/110	1.22	8.11	1.160	Arsphenamine jaundice
23	9.7	225/57	2.34	1.50	1.160	Arsphenamine jaundice
24	8.8	260/55		0	1.160	Arsphenamine jaundice
25	8.4	260/96	1.79	4.40	1.40	Arsphenamine jaundice
26	6.7	175/45	2.20	3.96	1.160	Arsphenamine jaundice
27	6.6	310/110	0.50	8.76	1.160	Arsphenamine jaundice

TABLE 3—Jaundice Due to Extrahepatic Obstruction

Case No	Lactic Acid Retention After 30 Min, Mg per 100 Cc	Ratio of Total Cholesterol to Cholesterol Ester	Excretion of Hippuric Acid (Sodium Benzoate Test), Gm in 4 Hr	Excretion of Galactose, Gm in 5 Hr	Excretion of Urobilin	Diagnosis
1	0	830/470	3.37	3.60		Cancer of head of pancreas
2	0	425/150	0.80	0		Stone in common duct
3	0	415/220	1.50	1.08		Cancer of head of pancreas
4	0	430/110	3.15	0	1.7	Stone in common duct
5	9.7	225/57	2.34	1.50	1.160	Cancer of head of pancreas
6	4.0	270/78		0.90	0	Stone in common duct
7	4.8	385/170	0.82	1.80	1.40	Cancer of gallbladder and ducts
8	1.0	580/227	Positive	3.30	1.5	Cancer of head of pancreas
9	3.6	356/170		0.96	1.10	Stone in common duct
10	3.3	155/36		0	1.4, 1.640, 1.2	Stone in common duct
11	1.0	275/200	1.90	0.40	1.20	Stone in common duct
12	0.7	375/155	2.06	0.27	1.10	Cancer of gallbladder and ducts
13	1.4	440/250	3.79	0.69	1.80	Stone in common duct

TABLE 4—Diabetes and Myopathies

Case No	Retention of Lactic Acid After 30 Min, Mg per 100 Cc	Blood Sugar, Mg per 100 Cc	Diagnosis
1	5.2	150	Diabetes
2	0	194	Diabetes
3	0	545	Diabetes
4	0	200	Diabetes
5	0	250	Diabetes
6	0		Myasthenia gravis
7	6.8		Myasthenia gravis
8	2.7		Polymyositis
9	0		Pseudohypertrophic muscular dystrophy
10	2.4		Myasthenia gravis
11	0.1		Amyotonia congenita

Since the test mirrors one phase of carbohydrate metabolism, it is important to determine what influence the presence of diabetes has on the results. Table 4 presents the data for 5 patients with diabetes of mild, moderate or severe intensity. The first patient, with a blood sugar value of 150 mg per hundred cubic centimeters during fasting, showed a retention of 5.2 mg per hundred cubic centimeters of lactic acid above the control level. This patient, however, had a large liver, which extended to the level of the umbilicus. The remaining 4 patients, despite considerable elevation of the blood sugar level, utilized the injected sodium *d*-lactate in a normal fashion. In this table are also recorded the results obtained in 6 instances of various types of myopathy. One of this group, a patient with myasthenia gravis, showed retention of 6.8 mg per hundred cubic centimeters.

In table 5 are charted for purposes of comparison the results obtained with several other hepatic function tests performed on the group of

TABLE 5—*Hepatitis and Jaundice Due to Extrahepatic Obstruction*

	Cases of Hepatitis			Cases of Jaundice Due to Extrahepatic Obstruction		
	Total No of Cases	Positive Results	Negative Results	Total No of Cases	Positive Results	Negative Results
Sodium <i>d</i> lactate test	27	26	1	12	1	12
Determination of ratio of total cholesterol to cholesterol ester	25	12	13	13	4	9
Galactose tolerance test	26	14	12	13	2	11
Sodium benzoate test	23	22	1	10	7	3
Urobilin test	10	10	3	10	3	7

patients with hepatitis and with jaundice due to extrahepatic obstruction. The tests that were made simultaneously with the sodium *d*-lactate test were the determination of the ratio of total cholesterol to cholesterol ester, the sodium benzoate test, the galactose tolerance test and the test of the urinary excretion of urobilin.¹⁰ It will be seen that in the patients with hepatitis the sodium *d*-lactate and the sodium benzoate test yielded the greatest incidence of positive results, while the galactose tolerance test and the determination of the ratio of total cholesterol to cholesterol ester showed hepatic damage in only approximately half the instances. For the group of patients with obstructive jaundice, however, the results obtained with the sodium benzoate test were misleading, since in 10

10 The following values for the tests employed were accepted as evidence of hepatic dysfunction: for the proportion of cholesterol ester, a value of 40 per cent or less, for the sodium benzoate test, a urinary excretion of less than 3 Gm of hippuric acid during a four hour period, for the galactose tolerance test, a urinary excretion of 3 Gm or more of galactose during a five hour period, and for the test for urobilinuria, a urinary excretion of urobilin in dilutions of 1:20 or higher.

instances of proved extrahepatic obstruction with icterus, the latter tests yielded 7 positive results, that is, in 7 instances the sodium benzoate test suggested extensive hepatic damage

Of this group of 13 patients with obstruction, the results with the sodium *d*-lactate test were negative for 12, and the results of the galactose tolerance test were negative for 11, whereas the determination of the ratio of total cholesterol to cholesterol ester indicated no hepatic damage in 9 instances

COMMENT

It would hardly seem fair to add another hepatic function test to the already overcrowded diagnostic armamentarium unless it could serve a definite purpose. The different types of hepatic function tests and their respective merits have been adequately reviewed before¹¹. In a general way, it may be said that in the absence of jaundice there are several satisfactory procedures which may help in determining the presence or absence of hepatic dysfunction. In the presence of jaundice, however, the problem is much more involved. The number of tests which are available are limited and unfortunately are not entirely satisfactory. The jaundiced patient not infrequently presents the diagnostic problem as to whether the jaundice is due to extrahepatic obstruction or to intrinsic disease of the hepatic parenchyma. The group of patients with jaundice due to extrahepatic obstruction not infrequently have slight hepatic damage, which may be determined by a test such as the sodium benzoate test, hence this procedure is not very helpful in the making of a differential diagnosis. The galactose tolerance test and the determination of the ratio of total cholesterol to cholesterol ester are less sensitive, but unfortunately so often give negative results for patients with hepatitis that here again their value is reduced. The ideal test would be one which is sensitive enough to yield positive results in the presence of diffuse hepatic parenchymal damage but which would give uniformly negative results when the jaundice is due to extrahepatic obstruction. As to how closely the sodium *d*-lactate test approximates this ideal will be determined in time by more extensive investigations in other clinics.

We have not employed this test for patients with hepatic disease in the absence of jaundice, since there are so many satisfactory tests available under such circumstances. Our object in introducing this test is to provide another means which may help in differentiating jaundice due to disease of the hepatic parenchyma from jaundice due to extrahepatic obstruction.

11 Soffer, L. J. Present Day Status of Liver Function Tests, *Medicine* **14** 185, 1935. Snell, A. M., and Magath, T. B. The Use and Interpretation of Tests for Liver Function, *J. A. M. A.* **110** 167 (Jan 15) 1938.

CONCLUSIONS

The utilization of intravenously injected sodium *d*-lactate as a hepatic function test is described

Seventy-five milligrams per kilogram of body weight of this substance is injected intravenously, and a retention of 5 mg or more per hundred cubic centimeters above the control level for the lactic acid content of the blood at the end of one-half hour is considered abnormal

The major field of usefulness of this test is in the differentiation of jaundice due to diffuse disease of the hepatic parenchyma from jaundice due to extrahepatic obstruction

The test was performed on 76 persons, 25 of whom were normal. There were 5 patients with diabetes and 6 with various types of myopathy. There were 40 patients with jaundice, 27 of whom had diffuse hepatic damage, such as catarrhal and arsphenamine jaundice, while 13 had jaundice due to extrahepatic obstruction, confirmed either at operation or at necropsy.

In normal persons the degree of retention of the injected sodium *d*-lactate was less than 5 mg per hundred cubic centimeters, while in 1 diabetic patient and in 1 patient with myasthenia gravis there was a retention of more than 5 mg per hundred cubic centimeters. The diabetic patient who showed this abnormal retention had a considerably enlarged liver.

Of the 27 patients with icterus due to hepatitis, all with the exception of 1 patient showed an abnormal retention of the injected lactate.

In only 1 of the 13 patients with jaundice due to extrahepatic obstruction was there an abnormal retention of the injected lactate. This patient had severe cholangitis, with associated injury of the hepatic cells confirmed by biopsy.

Comparative studies were made for all the patients with jaundice with the sodium benzoate test, the galactose tolerance test, the urobilinuria test and the determination of the ratio of total cholesterol to cholesterol ester.

In comparing the results obtained with the sodium *d*-lactate test and those obtained with the various other hepatic function tests it was found that the first-mentioned test was most helpful in differentiating between the two types of jaundice.

HEPATIC COMPLICATIONS IN POLYCYTHAEMIA VERA

WITH PARTICULAR REFERENCE TO THROMBOSIS OF THE HEPATIC
AND PORTAL VEINS AND HEPATIC CIRRHOSIS

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Patients with polycythaemia vera commonly first consult a physician because of vascular thromboses¹. The frequent situation of these lesions in cerebral, peripheral and intra-abdominal vessels is well recognized. The clinical picture is essentially determined by the vitality of the organ deprived of its blood supply. An opportunity was recently afforded to study a patient with polycythaemia vera in whom huge enlargement of the liver, ascites and jaundice supervened owing to thrombosis of the hepatic veins. Because of the rarity of this complication, the difficulties in making a differential diagnosis and the gravity of the prognosis, this case was deemed worthy of recording, and the pertinent literature was surveyed.

REPORT OF A CASE²

History—A Jew aged 30 years entered the hospital because of increasing shortness of breath, weakness and abdominal enlargement. He had measles, mumps and diphtheria in childhood. Tonsillectomy was performed uneventfully seven years previously. Varicose veins of a few years' duration were given injection treatment unsuccessfully two years before entry.

The patient had always had a ruddy complexion and was perfectly well until three weeks prior to entry, when for no apparent reason, generalized abdominal cramps and severe diarrhea, consisting of fifteen to twenty watery stools daily, developed. The stools contained no blood, mucus or pus. The diarrhea spontaneously gave way to constipation. With the onset of the diarrhea, progressive enlargement of the abdomen was noted, soon becoming associated with shortness of breath. In addition, the patient complained of constant epigastric distress, weakness, loss of appetite and profuse sweating. For two weeks the eyes had been yellow and the urine dark. A low grade fever, with a rise in temperature to 100 F, was also noted.

Examination—The patient weighed 222 pounds (100.7 Kg). There had been a recent gain of over 20 pounds (9 Kg). He was well developed and well nourished but appeared acutely ill and obviously dyspneic. While there was no cyanosis, the skin of the malar region, ears, tip of the nose and palms was distinctly ruddy. The eyes were bloodshot, and the mucous membrane of the tongue,

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1 Brown, G. E., and Giffin, H. Z. Peripheral Arterial Disease in Polycythemia Vera, Arch Int Med 46:705-717 (Oct) 1930

2 In table 1 this case is referred to as case 60

cheeks and throat was brick red. The skin and scleras were moderately icteric. The pupils were normal. Examination of the fundus disclosed engorged veins. No abnormality was present in the structures of the neck. Marked dulness-to-flatness, diminished breath sounds and fremitus were present over the basal portions of the lungs posteriorly, especially on the right side. The left cardiac border was percussed just outside the nipple line. The heart sounds were of fair quality, and no murmur was present. The blood pressure was 120 systolic and 90 diastolic. The radial pulses were of poor quality.

The abdomen was markedly distended with fluid. The liver was markedly enlarged, slightly tender and smooth, and its edge was palpable 5 fingerbreadths below the right costal margin. The spleen was not felt. Rectal examination revealed only a few external hemorrhoids. Bilateral varicosities of the internal saphenous system in each leg were present. There was no edema, and pulsations were felt in both dorsalis pedis arteries.

Laboratory examinations (the hematologic studies were made by Dr. Frank Bassen) disclosed the presence of polycythaemia vera. A blood count showed hemoglobin, 110 per cent (Sahl), erythrocytes, 7,430,000 per cubic millimeter, platelets, 220,000, leukocytes, 29,500, polymorphonuclear neutrophilic leukocytes, 82 per cent (segmented forms, 79 per cent), eosinophilic leukocytes, 2 per cent, lymphocytes, 13 per cent, mononuclear cells, 2 per cent, and myelocytes, 1 per cent. The blood volume was 9,750 cc, representing a volume of 108 cc per kilogram. The relative cell volume was 60 per cent. The urine contained a trace of albumin, a faint trace of bile and urobilin and occasional leukocytes. Occult or gross blood was absent from the stool. The icteric index of the blood (acetone method) was 22, and there was a faint delayed positive direct van den Bergh reaction. The serum bilirubin value was 4 mg per hundred cubic centimeters. Marked hepatic damage was indicated by the plasma cholesterol value of 125 mg, with only a trace of ester fraction, and the blood sugar value of 50 mg. The urea nitrogen content of the blood was 13 mg. The Wassermann test of the blood gave a negative reaction. A roentgenogram of the chest disclosed large pleural effusions at the base of each lung, more extensive on the right side.

It was felt that the patient was suffering from polycythaemia vera with complicating portal obstruction. The tremendous enlargement of the liver appeared to exclude simple thrombosis of the portal vein as the cause. The degree and rapidity of the hepatic enlargement and the advanced hepatic damage, as evidenced by the extremely low cholesterol partition, seemed to justify the diagnosis of obstruction of the hepatic veins. In view of the primary polycythemia, it was felt that the obstruction was a completely occlusive thrombosis.

Course—After abdominal paracentesis, with the removal of 6,100 cc of bile-stained fluid, the patient became drowsy, mentally confused and profoundly weak. The blood cholesterol value sank to 62 mg, with absence of ester. Profuse drainage continued from the abdominal wound for a week. With a high carbohydrate diet, daily hypodermoclyses of 5 per cent solution of dextrose and a restricted intake of fluid and salt, his general condition began to improve, the icterus disappeared, his appetite and strength partially returned and the blood cholesterol value rose to 100 mg, although the ester fraction was still absent. The improvement came about despite the fact that two phlebotomies of 450 and 400 cc, respectively, failed to influence the blood count. Notwithstanding a continued increase in the patient's sense of well-being with a concomitant rise in the blood cholesterol value to 140 mg, with no ester, edema of the feet and legs appeared, and peritoneal fluid reaccumulated, requiring a second paracentesis (2,400 cc).

Hematologic values at this time were essentially unaltered, and a third phlebotomy (650 cc) was performed, with a resultant drop of the hemoglobin value to 94 per cent and of the erythrocyte count to 5,260,000. The leukocyte count remained at 18,200 per cubic millimeter. Thereafter, ascites gradually reappeared, the cholesterol value mounted to 185 mg, with 50 mg of ester, and a third paracentesis was performed. No diuresis followed three intravenous injections of mercurin with theophylline. The patient was discharged from the hospital nine weeks after entry with only a small amount of fluid in the abdominal cavity, a blood cholesterol value of 215 mg, with 35 mg of ester, a hemoglobin value of 102 per cent, an erythrocyte count of 5,980,000 and a leukocyte count of 27,500 per cubic millimeter. The total protein content of the blood was 6.1 Gm per hundred cubic centimeters, of which serum albumin constituted 4.2 Gm and globulin 1.9 Gm.

The patient survived for over two months. Two weeks after discharge from the hospital he was readmitted for abdominal paracentesis (4,700 cc) and Potain aspiration (1,600 cc) of the right pleural cavity. A blood count showed hemoglobin, 103 per cent, erythrocytes, 5,420,000, and leukocytes, 14,500 per cubic millimeter. The blood cholesterol value was 150 mg, with 17 mg of ester. The patient was ambulatory and fairly comfortable except for occasional periods of abdominal cramps and diarrhea. He reentered the hospital for the third time three weeks later, a week before death. The fifth and final abdominal paracentesis (5,000 cc) was performed. It was of interest that the blood count had remained stationary at relatively normal levels for the three months following the last phlebotomy, without any recurrence of the polycythemic state. The blood cholesterol value was then 175 mg, with 26 mg of ester. The scleras again became slightly icteric, and bile and urobilin were again present in the urine. The patient had steadily lost ground, and although the abdomen was still protuberant, he presented evidences of marked loss of weight, with pinched facies. During the entire period of observation the liver did not vary in size, while the spleen could be occasionally and indefinitely palpated.

It was felt that recanalization of the thrombosis of the hepatic veins, possibly with hepatic regeneration, had occurred to some extent, because of the initial clinical improvement and the increase of the cholesterol values and partition. In view of the hopeless prognosis and the probability that adequate time for the maximum development of recanalization and parenchymal regeneration had elapsed, omentopexy, with the patient under procaine hydrochloride infiltration anesthesia, for the purpose of shunting the portal circulation was performed. The surgical procedure was tolerated well, but about twelve hours after operation the patient showed signs of shock and died. This occurred almost five months after the onset of symptoms.

Postmortem Examination (Drs. Bernheim and Seligmann)—The anatomic diagnosis included obliterating organized thrombosis of the hepatic, portal, splenic and superior mesenteric veins with recanalization, a localized organizing mural thrombus in the intrahepatic portion of the inferior vena cava, extreme passive congestion of the liver, hepatic degeneration, ascites, hydrothorax, and peripheral edema.

The liver weighed 2,975 Gm. Its surface was light red and mottled with small yellow flecks and occasional darker congested areas. It was smooth except for the lateral portion of the right lobe, where distinct nodules, 2 to 5 mm in diameter, were present. On section the periportal zones were markedly increased in size. The central areas were dark red, enlarged and markedly depressed. Numerous branches of the hepatic veins were occluded by grayish or grayish red tissue. On microscopic examination the normal appearance was greatly

impaired. The capsule was infiltrated with lymphocytes and mononuclears. This infiltration was also present in the portal areas. In addition, the radicles of the portal vein in the portal spaces were markedly dilated. Most of the hepatic tissue was destroyed. Except for a thin rim of parenchymal cells which contained fat, immediately surrounding the portal fields, only blood-filled and empty sinusoids and stroma were recognizable. In the destroyed areas, fat droplets were seen within the Kupffer cells. The fibers of the reticulum were collapsed, slightly thickened and fragmented in the intermediate and central portions of the lobules. The central veins were engorged. In some instances their walls were somewhat thickened. A moderate number of sublobular veins showed partial or complete occlusion by young cellular connective tissue, occasionally with recanalization. A large hepatic tributary was seen to be occluded by loose, spongy connective tissue, the interstices of which contained blood. In addition, there were within the occluded lumen a few thin-walled vessels, indicating recanalization of an organized thrombus. The internal elastic membrane of the large vein was for the most part intact. Here and there it was broken by penetrating vessels. No evidence of inflammation was found in the wall of the vein.

The spleen weighed 1,125 Gm. Microscopic examination revealed marked congestion, with hyperplastic sinusoids. Hemorrhage and increased numbers of polymorphonuclear leukocytes were present in the perifollicular regions. Near the follicles, periarterial fibrosis was noted. Occasional localized areas of fibrosis were present with marked fibrous thickening of the Billroth cords.

The bone marrow was red and hyperplastic, typical of polycythaemia vera, with striking erythropoiesis. Microscopically there was an increased number of normoblasts and megakaryocytes.

Comment—Observation of this case stimulated interest in the subject of hepatic manifestations in polycythaemia vera. This resolved itself principally into an inquiry into the incidence and pathogenesis of hepatic enlargement, ascites and jaundice.

HEPATIC ENLARGEMENT IN POLYCYTHAEMIA VERA

The vascular bed of the liver, like that of the other organs in polycythaemia vera, is markedly distended with blood. Microscopically, marked congestion of the veins is noted, often with some atrophy of the adjacent hepatic cords. Clinical enlargement of the liver has been observed in the majority of the cases. Brown and Giffin³ found it in 8 of 14 cases. In order to obtain further data concerning the incidence and significance of hepatic enlargement in this disease, a study was made of 59 additional patients with polycythaemia vera admitted to the hospital wards between 1919 and 1937 (table 1). Seven of these patients came to necropsy. All had definite polycythaemia vera, characterized by typical blood values,⁴ splenomegaly or hyperplastic bone marrow. Furthermore, the absence of an increased demand for oxygen in these

3 Brown, G. E., and Giffin, H. Z. Studies of the Vascular Changes in Cases of Polycythemia Vera, *Am J M Sc* **171** 157-168, 1926.

4 Almost all the blood counts and determinations of the blood volume were performed by Dr. Nathan Rosenthal or members of his department.

cases excluded secondary polycythemia. Particular attention was paid to the duration of symptoms, the palpability of the liver and spleen, the effect of treatment, the blood count, volume and cholesterol value, and the presence of icterus, ascites, vascular lesions and associated diseases.

Hepatic enlargement was considered slight if the edge of the liver was palpable 1 fingerbreadth, moderate if 2 or 3 fingerbreadths and marked if more than 3 fingerbreadths below the costal margin. In 22 cases the liver was not palpable or enlarged, in 8 cases enlargement was slight, in 17 cases moderate and in 13 cases marked. Thus, in 50 per cent of the cases there was moderate or marked enlargement of the liver.

When the cases were grouped according to the degree of hepatic enlargement, a general correlation with the duration of polycythemic symptoms was noted. The average duration of symptoms was two and three-tenths years when enlargement of the liver was absent, three and six-tenths years when it was slight, four and three-tenths years when it was moderate and five and one-tenth years when it was marked. It should be noted, however, that these figures represent averages for groups and that extreme exceptions are readily noted. For example, in 3 cases in which hepatic enlargement was absent or slight (cases 11, 59 and 33), the duration of symptoms was ten, eleven and twelve years. On the other hand, in cases 22, 43 and 60 there was marked enlargement of the liver, with a minimal duration of symptoms. In this connection, however, cognizance must be taken of the fact that polycythemia vera often exists for many years without producing symptoms. This imposes a serious limitation on the interpretation of this correlation.

As several patients were observed for prolonged periods, changes in the size of the liver were frequently noted. No consistent effect of treatment on the size of the liver was found, irrespective of the type of treatment or the effect on the blood count and symptoms. In general, the liver increased in size with the passage of time, despite treatment. Intercurrent icterus induced by phenylhydrazine (cases 25, 29 and 48) was usually associated with a rapid increase in the size of the liver. In 2 (cases 29 and 48) of these 3 cases, the liver receded to its previous size as the jaundice disappeared. In another instance (case 53) a decrease in size was noted while the patient was under treatment. The liver was found to be smaller some time after discontinuance of treatment in 3 other cases (cases 49, 51 and 59). Terminal decrease in the size of the liver was observed in the presence of complicating cirrhosis (case 54).

A study of the tabulated data disclosed no general relation between hepatic and splenic enlargement except so far as marked splenomegaly was concerned. This occurred in 5 of 30 cases in which hepatic enlargement was absent or slight, in 6 of 17 cases in which hepatomegaly was

TABLE 1—Clinical Findings in Sixty Cases of Polycythaemia Vera Grouped According to the Degree of Hepatic Enlargement

Case	Age	Sex	Duration	Palpability		Hemo- globin, %	Erythro- cytes, million per Cu Mm	Platelets	Leuko- cytes	Blood Volume, Cc per Kg	Choles- terol, Mg per 100 Cc †	Vascular Thrombosis	Comment
				Liver	Spleen*								
No Hepatic Enlargement (22 Cases)													
2	30	M	For years	0	3 f	170	980		8,000				
4	40	F	3 mo	0	3 f	120	710		13,600				
5	35	F	4 mo	0	4 f	154	935	449,000	12,000	193			
				Barely†	4 f	123	892	250,000	8,800				
6	28	M	1 yr	0	0	125	760	450,000	8,800	113		Digital	
7	51	M	0	Barely	Barely	140	776	17,200	17,200		215		
9	51	M	3 yr	Indefinite†	At level of umbilicus	135	786	16,400	16,400				
						112	650	14,800	14,800		120		
11	65	F	10 yr	0	Below iliac crest	130	700	16,400	16,400				
13	63	M	4 yr	0†	2 f	140	970	360,000	12,000	220		Previous hemiplegia, later, popliteal artery	
15	55	F	0	0	0	138	1035		7,800	123			Died after cholecystec- tomy
16	60	M	0	0	1 f	104	725		9,000	122		Subclavian vein, cerebral	
17	41	M	6 yr	0	3 f	135	820	300,000	13,000				
21	62	F	6 mo	0	23 f	126	900	380,000	10,600		170		
23	56	F	6 yr	0	3-4 f	140	935	290,000	21,600	133			Diabetes
24	32	M	0	0	0	128	644	610,000	25,800	190			Coronary disease
26	62	M	2 yr	0	3 f	130	839	650,000	18,600	170			Coronary disease, gout
											150/35 135/25 195		Anerythremic phase (no treatment for 1 year)
27	66	M	6 yr	0†	4 f	55	610	600,000	46,000				Died
28	48	M	5 yr	0†	2 f	150	950	440,000	36,000				
31	49	M	5 mo	0	3 f	145	850	340,000	10,600	224			
37	46	M	0	Barely	1 f	135	1380	560,000	9,400	168			
38	32	F	2 yr	0†	3 f	105	820	17,200	17,200				
39	66	M	8 mo	0	0	135	772	370,000	11,000	120			
46	42	M	1 yr	0	1 f	123	961	20,000	20,000				
					0	125	864	7,900	7,900				
Slight Hepatic Enlargement (8 Cases)													
12	31	M	0	12 f	12 f	132	685		5,000	105		Peripheral	
18	49	F	2 yr	1 f	1 f	132	750	130,000	6,900		216	Peripheral	
33	40	F	12 yr	2 cm	At level of umbilicus	140	925	300,000	11,600	172	215	Cerebral	
44	66	F	0	1 f	3 f	122	870	700,000	15,000	127		Common iliac veins	
53	60	M	1 yr	1 f	3 f	130	830	290,000	22,200			Digital	
				0†	2 f	123	828	280,000	34,800				
56	43	M	0	1 f	0	129	1090	300,000	15,000				Necropsy: uric acid, cal- culous hydronephrosis with anuria
													Necropsy: status post nephrectomy for carcinoma
58	55	M	5 yr	1 f	0	135	1025		11,500			Cerebral Coronary artery	Necropsy: cerebral thrombosis, old closure of left coro- nary artery

TABLE 1—Clinical Findings in Sixty Cases of Polycythaemia Vera Grouped According to the Degree of Hepatic Enlargement—Continued

Case	Age	Sex	Duration	Palpability		Hemo- globin, %	Erythro- cytes, million per Cu Mm	Platelets	Leuko- cytes	Blood Volume, Cc per Kg	Jaun- dice	Choles- terol, Mg per 100 Cc†	Vascular Thrombosis	Comment
				Liver	Spleen*									
Marked Hepatic Enlargement (13 Cases)														
8	51	M	2 yr	Half way to umbilicus	At level of umbilicus	150	• 10 61		12,800					
19	56	F	3½ yr	At level of umbilicus	umbilicus	132	11 15	290,000	9,600				Cerebral	
22	66	M	6 mo	5 f	3 f	109	6 40		25,000				Peripheral	
30	67	F	8 yr	At level of umbilicus	Almost to umbilicus	130	8 10	450,000	38,200					
41	34	F	1 yr	At iliac crest	At level of umbilicus	102	6 00	640,000	60,000	141		115/0	Previous cerebral	Leukemic transformation
42	43	M		0	5 f	112	9 11		10,200			166		
53	53		10 yr	At level of umbilicus	At iliac crest	128	8 10	350 000	16,800	154		180/52		
43	60	F	0	At level of umbilicus	1 f	116	6 82		36,000			234/70		
47	55	F	7 yr	4 f	2 f	128	8 25		14,600					Anerythemic phase
54		F	0		2 cm	160	8 16		12,000					
56			9 yr	1 f†	2 f	155	7 83	200,000	14,000	174	+	275/ 75 310/ 75 500/170		Phenylhydrazine jaundice
				At level of umbilicus,†	1 f									
				later, 4 f										
51	35	F	1 yr	Almost at umbilicus	3 f	118	9 13	790,000	15,000					Asaides and edema responded to mercurin with theophylline
	40		6 yr			105	9 70				+	420/235		Died from hemorrhagic neeropsy toxic cirrhosis
55	41		7 yr	4 f	Not felt (asites)	55	3 43		48,000					Asaides and edema of cardiac failure, ne- eropsy coronary disease
	60	F	5 yr	4 f	5 f	130	8 00	456,000	19,900					
	65					89	4 70	840,000	50,000					
57	49	M	17 yr	2 f	5 f	133	11 00		32,000				Cerebral	Neeropsy leukemic transformation
52	52		20 yr	4 f	2 f below umbilicus	109	7 35	250,000	50,000					Neeropsy, thrombosis of hepatic, portal, splenic and superior mesenteric veins
60	30	M	0	5 f	0 (asites)	110	7 43	220,000	29,500	108	+	125/trace 62/0, 100/0, 140/0, 185/50, 215/35	Hepatic veins, etc	

moderate and in 7 of 13 cases in which it was marked. In other words, there is a tendency toward association of marked enlargement of the liver and spleen.

No correlation could be established between the size of the liver and the hemoglobin value, the erythrocyte, leukocyte or platelet count or the volume of blood per kilogram of body weight. The plasma cholesterol value was determined in 22 cases and bore no definite relation to the size of the liver or the presence of jaundice. The group of patients with marked hepatomegaly presented the widest variation of cholesterol values.

Vascular lesions occurred one or more times in 21 of the 60 patients. This corresponds to the findings of Norman and Allen,⁵ who reported vascular lesions in about one third of 98 patients seen at the Mayo Clinic. Vascular thrombosis in the present series was not related to the degree of hepatic enlargement.

Finally, certain associated diseases appeared to have some effect on the size of the liver. A spontaneous anerythremic phase was observed in 2 instances in which hepatic enlargement was moderate, although it also occurred in 1 case without enlargement of the liver. Moderate or marked enlargement of the liver with jaundice was due to phenylhydrazine in 4 cases. Overactivity of the myeloid elements of the hemopoietic system with leukemic transformation was present in 2 cases of moderate and 2 others of marked hepatic enlargement. Cardiac decompensation, cirrhosis of the liver and complete thrombosis of the hepatic and portal veins were associated with marked hepatic enlargement and ascites.

From the foregoing data it is evident that in about two thirds of the cases of polycythemia vera the liver may be palpated while in one half there is moderate or marked hepatic enlargement. Simple engorgement with blood is undoubtedly a factor. In many instances the degree of hepatic enlargement appears to be related to the duration of the disease. In some cases in which there is considerable enlargement of the liver, associated diseases play a dominant role. These conditions, which may be regarded as secondary complications, comprise phenylhydrazine jaundice, leukemic transformation, myocardial decompensation, cirrhosis of the liver and thrombosis of the hepatic and portal veins.

The clinical diagnosis of phenylhydrazine jaundice, leukemic transformation or myocardial failure is usually made without difficulty. However, hepatic cirrhosis or thrombosis of the portal or hepatic veins, with or without ascites, is generally diagnosed only at the necropsy table. In an attempt to elucidate the clinical picture of these complications, the literature was searched for similar conditions. Only authentic cases in which the diagnosis was proved at autopsy were selected.

⁵ Norman, I. L., and Allen, E. V. The Vascular Complications of Polycythemia, *Am Heart J* **13** 257-274, 1937.

CIRRHOSIS OF THE LIVER IN POLYCYTHAEMIA VERA

While Harrop⁶ has stated that hepatic cirrhosis is a rather common terminal event in polycythaemia vera, others⁷ have viewed it as a rarity. There are but 9 acceptable instances reported in the literature (table 2).⁸ In spite of the relatively small number of cases reported, there can be no doubt that the association of polycythaemia vera with cirrhosis is more than a simple coincidence. All writers have acknowledged an etiologic relation between the two conditions, although they have not always been in agreement concerning the precedence of the polycythemia or of the cirrhosis.

Turk,⁹ credited with the first report, said he believed that the cirrhosis is the primary condition. A toxic effect on the blood was hypothesized to explain induced overactivity of the bone marrow resulting in polycythemia. This theory appeared to receive some support subsequently from the experimental work of Hess and Saxl,¹⁰ who produced erythrocytosis by means of hepatotoxic agents. They gave as their opinion that a primary alteration in the cells of the liver (cirrhosis) produces an impairment of its hemoglobin—destroying function with resultant polycythemia.

A contrary mechanism was first suggested by Mosse,¹¹ who said he regarded hepatic cirrhosis as a secondary complication of polycythaemia vera. He concluded that increased destruction of blood and an excessive amount of blood in the liver are the primary etiologic factors resulting in hepatic damage. Most workers now adhere to this point of view.

Analysis of the available reports of 10 cases (including case 54) reveals the fact that hypertrophic, atrophic, "toxic" (Mallory type) or

6 Harrop, G. A., Jr. Polycythemia, *Medicine* **7** 291-344, 1928.

7 (a) Uhlhorn, E. Ueber Polycythämie mit Lebercirrhose, *Klin Wchnschr* **11** 2037-2038, 1932. (b) Weber, F. P. A Case of Erythremia with Jaundice, Hepatic Cirrhosis and Hematemesis, *Lancet* **1** 800-801, 1933.

8 Holt's (Holt, W. C. Erythremia [Polycythemia Vera]. A Report of a Case with Autopsy, *Virginia M. Monthly* **57** 472-474, 1930) case of "early cirrhosis" was not included because of the probable relation to the cardiac failure and chronic passive congestion of the viscera which were present. The freely quoted cases of Hess and Saxl¹⁰ were excluded because of the absence of any clinical data to indicate that the erythrocytosis was actually polycythaemia vera. Cases of cirrhosis secondary to thrombosis of the hepatic veins are discussed under that heading.

9 Turk, W. Beiträge zur Kenntnis des Symptomenbildes Polycythämie mit Milztumor und "Zyanose," *Wien klin Wchnschr* **17** 153-160 and 189-193, 1904.

10 Hess, L., and Saxl, P. Ueber Hämoglobinzerstörung in der Leber, Hämoglobinzerstörung in der menschlichen Leber, experimentelle Hyperglobulie, *Deutsches Arch f klin Med* **104** 1-15, 1911.

11 Mosse, M. Polyglobulie und Lebererkrankung, *Ztschr f klin Med* **79** 431-440, 1913.

TABLE 2—*Hepatic Cirrhosis in Polycythæmia Vera*

Author	Year	Sex	Age	Palpability		Ascites	Edema	Jaun dices	Hemo- globin, % per Cu Mm	Erythro cytes, Million	Leuko cytes	Necropsy Observations	
				Liver	Spleen							Liver	Hepatic, Portal and Other Veins
Turk, ^o case 7	1901	F	35	1 f	Greatly enlarged	0	0	+	20.1 Gm	7.36	12,100	Atrophy of left lobe with compensatory enlarge- ment of right lobe	
Blad, A., abstracted, Folia hæmat 2.685, 1903	1905	F	34	3 f	Markedly enlarged	0	0	0	115	11.00		Microscopically, begin- ning cirrhosis	
Hamilton, A. L., and Morse, M. E. Boston M & S J 166, 963 967, 1912	1912	F		Half way to umbilicus, decreased to normal size during obser- vation	Consider- ably en- larged	0	0	0	85	7.10		Toxic cirrhosis (Mal- lory type), weight, 1,555 Gm	
Mosso 11	1913	M	53	0	1 f below umbilicus	+	+	+	110	7.83	13,000	Atrophic cirrhosis	Thrombophlebitis of portal and splenic veins, enlarged medusæ
Schneider, P. München med Wchnschr 65 639 1918	1918	M	56	Palpable	Enlarged	0	0	+	150	8.50	7,600	Enlarged, weight, 1,900 Gm, microscopi- cally, mild cirrhosis with nodular regeneration	
Levl 12	1924	M	50									Normal size, no ascites	
Uhlhorn 7a	1932	F	78	0	5 f	+	0	+	110	8.70	49,700	Atrophic cirrhosis, weight, 1,430 Gm	Secondary organ- ized thrombosis of hepatic veins
Weber 7b	1933	F	40	3½ f Decreased to costal margin after hemorrhage and anemia	3 f	0	0	+	125	10.10	18,670	Fine cirrhosis	
Wilson, A. E., and Sprague, P. H. Canad M A J 33 167 168, 1935	1935	F	49	2 cm	2 cm	+	0	+	100	8.25		"Looks like cardiac cirrhosis," smaller than normal	
Caso 54 (unpublished data)		F	41	4 f	3 f	+	0	+	103	9.70	15,000	Toxic cirrhosis	

"fine" cirrhosis may occur in polycythaemia vera. Clinical enlargement of the liver and spleen is usually present and may be marked or even absent. A point of some importance is the notation in 2 cases of a recession in the size of the liver while the patient was under observation. Ascites was present in 4 cases, with associated edema of the legs in 1 case. In 1 case (case 54) diuresis was obtained by the use of a mercurial diuretic (mercurin with theophylline). Jaundice was observed in 7 cases. The blood studies were of no special relevance. Secondary thrombosis of the hepatic veins was noted by Uhlhorn.^{7a} Fibrosis of the liver (pseudocirrhosis) or possibly true cirrhosis with distortion of the lobular architecture may occur as a result of thrombosis of the hepatic veins and is discussed in that section.

The introduction of phenylhydrazine in the therapy of polycythaemia vera added another factor to be reckoned with in the etiology of cirrhosis. This hemolytic and hepatotoxic drug had been employed in the cases reported by Levi,¹² Weber^{7b} and Cole,¹³ but there is no definite evidence that it was responsible for the production of cirrhosis. Nevertheless, this drug has been shown experimentally to produce hepatic changes of a cirrhotic nature. Levi¹² stated the opinion that repeated courses of this chemical agent may result in cirrhosis in a case in which the liver has already been damaged by the noxious effects of polycythemia per se. The accuracy of this belief can be tested only in the course of time, during which data on additional cases, with and without phenylhydrazine therapy, can be accumulated.

THROMBOSIS OF THE PORTAL VEIN IN POLYCYTHAEMIA VERA

Polycythaemia vera is associated with thrombosis of the portal vein somewhat more frequently than it is with hepatic cirrhosis. Reports of only 13 accepted cases could be found in the literature (table 3).¹⁴ Lommel¹⁵ was the first to draw attention to the relation between thrombosis of the portal vein and polycythaemia vera. He concluded that chronic portal stasis could eventuate not only in splenic enlargement

12 Levi, E. Ueber die Ursache der Lebercirrhose bei Polycythämie. Leberschädigung durch Phenylhydrazintherapie, *Ztschr f klin Med* **100** 777-784, 1924.

13 Cole, N. B. Comments on a Case of Polycythemia Rubra Vera with Autopsy, *M. Clin North America* **16** 1255-1265, 1933.

14 Excluded because of lack of hematologic studies was Emmerich's¹⁶ case of cavernous transformation of the portal vein with ascites, splenomegaly and active hyperplastic bone marrow. The picture of the bone marrow was suggestive of polycythaemia vera. Cases 3 and 4 reported by Ludecke²² were also excluded because of insufficient evidence for the existence of polycythaemia vera. Two cases reported by Lubarsch and cited by Ludecke should be mentioned as a matter of record.

15 Lommel, E. Ueber Polycythämie mit Milztumor, *Deutsches Arch f klin Med* **87** 315-339, 1906.

TABLE 3—Thrombosis of Portal Vein in Polycythaemia Vera

Author	Year	Sex	Age	Palpability		Ascites	Edema	Jaundice	Hemo- globin, % per Cu	Erythro- cytes, Million Mm	Leuko- cytes	Necropsy Observations	
				Liver	Spleen							Liver	Portal, Hepatic and Other Veins
van der Weyde, A J, and van Lieren, W, ab- stracted, Münchener Med Wechschr 50 1979, 1903 Lommel 15	1906	M	42	2 f				0		760	12,800		Thrombosis of portal vein with dilatation of vessels in portal circulation and thick- ening of hepatoduodenal ligament
Versé, M. Beitr Path Anat u 526 530, 1910 Monro and Teacher 18	1910	M	29	At costal margin	Very large	0	0	0	140	823	11,000	Somewhat large	Dark brown thrombus in portal, splenic and superior mesenteric veins, hepato- duodenal ligament markedly thickened, into cavernous tissue, acute thrombus in superior mesenteric vein, with intestinal gangrene
Christian, H A Am J M Sc 154-547 554, 1917, case 1 Kratzeisen 10	1913	M	45	0	Enlarged	0	0	0				Not enlarged	Primary thrombophlebitis of great portal veins, oldest in splenic and in gastroepiploic veins, most recent thrombosis of portal vein and iliac region gangrene
Christian, H A Am J M Sc 154-547 554, 1917, case 1 Kratzeisen 10	1913	M	52	34 f	Consider- ably enlarged Readily palpable	0	0	0	120	640	20,400	Somewhat enlarged, "nutmeg type"	markedly increased vascularity of great portal veins, oldest in splenic and in gastroepiploic veins, most recent thrombosis of portal vein and iliac region gangrene
Sauer 30	1921	F	42	Not en- larged	Enlarged	0	0	0	97	620	22 200	Normal size	Old thrombosis of portal vein, acute thrombosis of mesenteric veins, with intes- tinal gangrene, cavernous transformation at hilus of liver and spleen
Horder 28	1926	M	53	Slightly enlarged	Very large	0	0	0	90	650	45,000	Somewhat enlarged	Acute postsplenectomy thrombosis of portal and mesenteric veins, with intes- tinal infarction
Brandberg 21	1926	M	45	0	Palpable	0	0	0	98	770	25,200	Normal size	Acute thrombosis of portal, splenic and superior mesenteric veins, with intes- tinal gangrene
Jacobi 20	1929	M	50		Very large	0	0	0	127	723	8 800	Normal size	Thrombosis of portal vein, acute throm- bosis of superior mesenteric vein, with intestinal infarction
Cole 11	1933	M	33	12 f, grad- ually reced- ing under costal margin	0	0	0	0	120	867	17,100	Normal size	Acute thrombosis of portal, splenic and mesenteric veins, with intestinal gangrene
Seggel 27	1937	M	27		+	+	+	145	780	13,200	20,500	Early erro- sis, probably secondary	Thrombosis of hepatic, portal and mes- enteric veins, with intestinal gangrene
Case 60	1938	M	30	5 f	+	+	+	110	743	20,500	2,975 Gm, extreme passive congestion	Organized thrombosis of portal, splenic and mesenteric veins, collateral circula- tion on abdomen Organized thrombosis with recanaliza- tion of hepatic, portal, splenic and mesenteric veins	

but in polycythemia as well. Emmerich,¹⁶ Reckzeh¹⁷ and Monro and Teacher¹⁸ stated the same opinion. Subsequently Kratzeisen¹⁹ introduced the reverse concept, namely, that thrombosis of the portal vein represents a complication of preexisting, often unrecognized polycythemia vera. Gruber,²⁰ Brandberg,²¹ Cole,¹³ Harrop⁶ and others also have subscribed to this point of view. There is little doubt that this is the actual sequence of events, when one considers the relatively high incidence of vascular occlusion in polycythemia vera. This depends on a heightened tendency to thrombosis (thrombophilia²²) based on several physiopathologic factors—increased blood volume, decreased velocity of blood flow,²³ increased viscosity of the blood, thrombocytopenia and hypercalcemia.²⁴ Thrombosis may be further favored by premature development of vascular sclerosis induced by excessive wear and tear by fluid of increased viscosity (Oppenheimer^{25a}) or by a disturbed intimal blood supply (Norman and Allen⁵).

Analysis of available reports of 14 cases shows that the liver was not enlarged clinically in at least 8. Of 2 patients with marked hepatic enlargement present clinically, 1 revealed a liver of normal size at necropsy (Chauffard and Troisier²⁶), while the other showed associated thrombosis of the hepatic veins (case 60). The liver was reported to be

16 Emmerich, E. Die kavernöse Umwandlung der Pfortader, Frankfurt Ztschr. f. Path. **10** 362-374, 1912.

17 Reckzeh, cited by Weber.⁴¹

18 Monro, T. K., and Teacher, J. H. Three Cases of Polycythemia, Lancet **1** 1015-1018, 1913.

19 Kratzeisen, E. Polycythämie und Pfortaderthrombose, Virchows Arch. f. path. Anat. **244** 467-492, 1923.

20 Gruber, G. B. Polyzithämie und Pfortaderthrombose, Centralbl. f. allg. Path. u. path. Anat. **33** 205-206, 1922-1923. Kratzeisen¹⁹ reported the same case.

21 Brandberg, R. Ueber das Verhältnis zwischen Polycythämie und Portalthrombose, Acta path. et microbiol. Scandinav. **3** 521-533, 1926.

22 Ludecke, H. Thrombophilie und Polycythämie, Virchows Arch. f. path. Anat. **293** 218-252, 1934.

23 Blumgart, H. L., Gargill, S. L., and Gilligan, D. R. Studies on the Velocity of Blood Flow. XV. The Velocity of Blood Flow and Other Aspects of the Circulation in Patients with "Primary" and Secondary Anemia and in Two Patients with Polycythemia Vera, J. Clin. Investigation **9** 679-692, 1931.

24 Brown, G. E., and Roth, G. M. The Reduction of Hypercalcemia in Cases of Polycythemia Vera Treated by Phenylhydrazine, J. Clin. Investigation **6** 159-169, 1928.

25 (a) Oppenheimer, B. S. Vascular Occlusion in Polycythemia Vera, Tr. A. Am. Physicians **44** 338-344, 1929. (b) Baehr, G., and Klemperer, P. Thrombosis of the Portal and of the Hepatic Veins, M. Clin. North America **14** 391-410, 1930.

26 Chauffard, A., and Troisier, J. Érythremie avec syndrome d'obstruction portale, Bull. et mem. Soc. med. d'hôp. de Paris **35** 610-622, 1913; Érythremie avec ascite, phlébite de la splénique et thrombose gastro-épiploïque, Presse med. **21** 653-655, 1913.

"somewhat large" at necropsy in 3 cases. Ascites and edema of the legs were present in 4 cases (in 2 of these there was associated thrombosis of the hepatic veins). A diuretic response to salyrgan was obtained in 1 instance.²⁷ Icterus was noted in 3 cases and was concurrent with ascites each time. The hematologic studies revealed the usual findings.

The pathologic details are of special interest. The thrombotic process was usually old and occasionally of many years' duration. However, in 3 instances the thrombus of the portal vein was fresh, the patients reported on by Horder²⁸ and Jacobi²⁹ presented the clinical appearance of sudden acute ileus or peritonitis, while in Sauer's³⁰ patient, acute thrombosis of the portal vein followed splenectomy. The majority of the patients succumbed with intestinal gangrene as a result of acute thrombosis of the mesenteric veins. In 5 instances the portal fissure or hepatoduodenal ligament was markedly thickened and so tremendously vascularized as to resemble cavernous tissue.³¹ This compensatory and collateral circulation was probably a factor in the prevention of ascites in each of these 5 cases. Large, dilated veins were present over the abdomen in 2 cases. In 2 instances organized thrombi were also found in the hepatic veins. In 1 of these cases there was associated secondary hepatic cirrhosis (Cole¹³).

According to Rolleston and McNee,³² hepatic cirrhosis is the most common cause of thrombosis of the portal vein. The latter as a primary lesion does not produce much hepatic damage. It is common to see some atrophy of the hepatic cells and replacement with fibrous tissue. This is not to be regarded as cirrhosis, in fact, there is little evidence that cirrhosis can arise in this manner.

Ascites occurs in about two thirds of all types of thrombosis of the portal vein. It is most likely to be absent in acute fulminating disorders or in cases of profuse diarrhea or gastrointestinal hemorrhage. A nonocclusive or recanalized thrombus or the presence of an extensive collateral circulation will likewise tend to prevent ascites. The low incidence of ascites in the cases of polycythemia may be related to a greater tendency toward the development of anastomotic circulation.

27 Seggel, K-A. Ueber besondere Verlaufsformen der Polycythämie vera, *Ztschr f klin Med* **132** 466-477, 1937.

28 Horder, T. Remarks upon Vaquez' Disease with Special Reference to Complications and with Notes of Seven Cases, *St Barth Hosp Rep* **59** 153-167, 1926.

29 Jacobi, A. Polycythämie und Mesenterialvenenthrombose, ihre Beziehungen zu Unfallverletzungen, *Mitt a d Grenzgeb d Med u Chir* **41** 555-561, 1929.

30 Sauer, H. Milzexstirpation bei Polyzythämia rubra (Morbus Vaquez), *Deutsche med Wchnschr* **50** 1641-1643, 1924.

31 A complete discussion of this lesion has been given by Klemperer.³³

32 Rolleston, H D, and McNee, J W. Diseases of the Liver, Gall-Bladder and Bile-Ducts, New York, The Macmillan Company, 1929.

(cavernous transformation of the hepatoduodenal ligament, caput medusae), possibly based on the altered hemodynamics present in polycythaemia vera. Ascites was mentioned in only 6 of 23 reports of cases of cavernous transformation of the portal vein collected by Klemperer³³

THROMBOSIS OF THE HEPATIC VEINS IN POLYCYTHAEMIA VERA

The hepatic veins appear to be one of the rarest and most important sites of venous thrombosis in polycythaemia vera. A careful search of the literature revealed reports of only 6 cases³⁴. The first authentic instance was reported by Oppenheimer²⁵ in 1929. Analysis of 7 available reports of cases (table 4) discloses clinical or postmortem enlargement of the liver in all but 1. This instance was one in which the thrombosis was secondary to preexisting atrophic hepatic cirrhosis. In another case of thrombosis of the hepatic veins associated with early (secondary) cirrhosis, the liver diminished in size while the patient was under observation (Cole¹³). The spleen was invariably enlarged. Ascites was present in all instances and accumulated rapidly in at least 3. In 2 cases diuretics were employed unsuccessfully. Edema of the lower extremities was noted in 5 cases. Jaundice occurred in 6 cases and was usually terminal. The blood counts were without special interest. Hydrothorax was present in 2 cases (the case reported by McAlpin and Smith³⁵ and case 60). The duration of life after the onset of ascites did not exceed six months.

Of special interest in case 60 were the plasma cholesterol values. Shortly after admission to the hospital the patient became profoundly weak and drowsy. At this time the plasma cholesterol value had fallen from 125 mg per hundred cubic centimeters, with only a trace of ester, to the extremely low value of 62 mg, with no ester fraction. Accompanying this was a drop in the blood sugar value to 50 mg per hundred cubic centimeters, indicating severe hepatic injury and a marked impairment of hepatic function. As the patient's condition improved, there was a corresponding rise in the plasma cholesterol value to 140 mg and finally to 185 mg, with 50 mg of cholesterol ester. This presumably

33 Klemperer, P. Cavernomatous Transformation of the Portal Vein. Its Relation to Banti's Disease, *Arch Path* **6** 353-377 (Sept.) 1928.

34 In 1880 Schuppel (Schuppel, O. *Die Krankheiten der Venae hepaticae*, in von Ziemssen, H. *Handbuch der speciellen Pathologie und Therapie*, Leipzig, F. C. W. Vogel, 1880, p. 323) reported a case of thrombosis of the hepatic veins and suggested that increased coagulability of the blood might have been the etiologic factor. This was some years before Vaquez described the disease, and no hematologic studies are available. Ludecke²² described 2 cases (cases 3 and 4) of thrombosis of the hepatic veins, but these are not included, because of insufficient evidence for the existence of polycythaemia vera.

35 McAlpin, K. R., and Smith, K. E. Polycythemia Vera. Report of Fourteen Cases Treated with Acetylphenylhydrazine, *New York State J. Med* **38** 101-108, 1938.

TABLE 4—*Thrombosis of Hepatic Veins in Polycythæmia Vera*

Author	Year	Sex	Age	Palpability			Asites	Edema	Jaundice	Hemo- globin, %	Erythro- cytes, Million per Cu Mm	Leuko- cytes	Necropsy Observations	
				Liver	Spleen								Liver	Hepatic, Portal and Other Veins
Oppenheimer, ^{25a} case 2	1929	F	19	3½ f	3 f		+	+	+	124	883	34,000	Extreme passive congestion	Organized, recanalized thrombosis in 2 main branches of hepatic vein supplying central two thirds of liver, portal vein free
Uhlhorn ^{7a}	1932	F	38	0	5 f		+	+	Terminal	110	870	49,700	Atrophic erythrosis	Old occlusive thrombosis of hepatic veins (secondary), portal vein free
Berk, L. Beitr z path Anat u allg Path 90 509 512, 1932, case 2	1932	F	56	Marked	Marked		+	+	Terminal	115	720	12,000	Enlarged, brown and red, with yellow spots	Old thrombosis of hepatic veins extending from mural thrombus in the inferior vena cava
Cole ¹³	1933	M	33	12 f, grad ually reced- ing under eos- tal margin	1 f		+	+	0	120	867	17,100	Early erythrosis, probably sec- ondary, central hemorrhage and necrosis	Thrombosis of hepatic and portal veins, mesenteric thrombosis, with intestinal gangrene
Norman and Allen ⁵	1937	F	54		Enlarged		+	+	Terminal				Markedly enlarged, acute passive congestion with central atrophy	Recanalized thrombosis of hepatic veins
McAlpin and Smith ³⁶	1938	F	57	Large	At costal margin		+	+	Terminal	125	680	8,300	Central hemor- rhagic necrosis, adenomas	Recent and organized thrombi in hepatic veins and branches
Case 60	1938	M	30	5 f	0 (asites)		+	+	Terminal	110	743	29,500	Markedly en- larged, weight, 2,975 Gm, exten- sive passive congestion	Organized thrombosis with recanalization of hepatic, portal, splenic and mesenteric veins

was conditioned by regeneration of the hepatic parenchyma and recanalization of the thrombosed hepatic and portal veins. The immediate prognostic significance of repeated plasma cholesterol and cholesterol ester determinations is well known³⁶ and was clearly brought out in this case.

The thrombi in the hepatic veins were invariably old and occlusive. In 3 cases recanalization was noted. Origin by extension from a mural thrombus in the hepatic portion of the inferior vena cava was claimed in 1 case. Antecedent atrophic cirrhosis was present in 1 case and secondary "early cirrhosis" in another. The portal vein was thrombosed in 2 instances.

Because of the rarity of occlusion of the hepatic veins, its clinical picture is not well recognized. Chiari³⁷ first drew attention to this lesion, and Hess³⁸ later collected reports of 24 cases in which chronic endophlebitis was the most common cause. Rolleston and McNee³² expressed the view that thrombosis of the hepatic veins is most frequently due to some other hepatic lesion.

When thrombosis of the hepatic veins occurs and is not secondary to hepatic disease, the resultant hepatic lesions comprise marked enlargement, with acute passive congestion and central hemorrhage, atrophy and necrosis. If the patient survives a sufficient length of time, the enlarged liver may develop a nutmeg appearance, with areas of atrophy, necrosis and regeneration. Subsequently, the liver is likely to shrink and become granular or nodular, owing to replacement of connective tissue and parenchymal hyperplasia. Thus, pseudocirrhosis (with preservation of the normal lobular architecture) may occur as a secondary lesion. Whether or not true cirrhosis with a completely distorted architecture can result from thrombosis of the hepatic veins is not clear from the few cases reported in the literature.

When thrombosis of the hepatic veins supervenes during the course of established cirrhosis, there may be little or no enlargement of the liver, depending on the previous size of this fibrotic nonexpansile organ.

Stasis in the portal vein³⁹ may be so marked as to induce thrombosis here, too. Ascites is an almost constant finding and characteristically

36 Epstein, E. Z., and Greenspan, E. B. Clinical Significance of the Cholesterol Partition of the Blood Plasma in Hepatic and in Biliary Diseases, *Arch Int Med* **58** 860-890 (Nov.) 1936.

37 Chiari. Ueber die selbständige Endophlebitis obliterans der Hauptstämme der Venae hepaticae als Todesursache, *Beitr z path Anat u z allg Path* **26** 1-18, 1899.

38 Hess, A. F. Fatal Obliterating Endophlebitis of the Hepatic Veins, *Am J M Sc* **130** 986-1001, 1905.

39 In acute experiments on dogs, Brandes (Brandes, W. W. The Effect of Mechanical Constriction of the Hepatic Veins with Special Reference to the Coagulation of Blood, *Arch Int Med* **44** 676-692 [Nov.] 1929) showed that mechanical constriction of the hepatic veins caused a rise in pressure in the portal vein to about twice the original value.

develops rapidly, as does the hepatic enlargement. Caput medusae, or dilatation of the veins on the abdominal wall, is frequently present in cases of prolonged involvement. Edema and anasarca are late manifestations. Icterus, commonly terminal in the cases of polycythemia, is uncommon in the other types. The course rarely exceeds six months, and the outcome is always fatal.

The differential diagnosis from cirrhosis of the liver and thrombosis of the portal vein is difficult. Prognostically the differentiation is important, as the outlook in thrombosis of the hepatic veins is graver than that in the conditions which simulate it.

COMMENT

While hepatic enlargement is common in polycythemia vera, the presence of marked enlargement frequently signifies an important complication. Phenylhydrazine jaundice, leukemic transformation and myocardial decompensation are not uncommon causes of considerable hepatic enlargement and are readily detectable. Cirrhosis of the liver and thrombosis of the hepatic and portal veins remain to explain a small number of cases, and the condition is usually diagnosed at necropsy. However, a study of the available reports of cases yields certain data which may prove useful in clinical diagnosis and therefore in prognosis. The latter is gravest when thrombosis of the hepatic veins is present.

Enlargement of the liver is practically constant (and typically rapid) in thrombosis of the hepatic veins, frequent in cirrhosis and uncommon in thrombosis of the portal vein (table 5). Recession in the size of the liver while the patient is under observation signifies either a spontaneous phenomenon, occurring in the natural course of uncomplicated polycythemia vera, or progression of a cirrhotic process in the liver. In the presence of ascites of noncardiac origin it strongly suggests cirrhosis.

Ascites is also constant (and likely to be of rapid development) in thrombosis of the hepatic veins, frequent in cirrhosis and uncommon in thrombosis of the portal vein.⁴⁰ The development of an extensive collateral circulation in the hepatoduodenal ligament was evidently sufficient in at least 5 cases of polycythemia with old thrombosis of the portal vein to prevent the formation of ascites. Mercurial diuretics appear to be ineffective in ascites due to thrombosis of the hepatic veins, while they seem to be successful when cirrhosis or thrombosis of the portal vein is present.

⁴⁰ That ascites of noncardiac origin may occur in polycythemia vera without cirrhosis or thrombosis of the hepatic or portal veins is evidenced by the case reported by Boyd (Boyd, W. The Relationship of Polycythemia to Duodenal Ulcer, *Am J M Sc* **187** 589-594, 1934). No cause for the ascites and icterus could be demonstrated at autopsy. Seggel²⁷ attributed the cause of ascites and icterus in such a case to circulatory disturbances in the liver.

Jaundice is common (and usually terminal) in thrombosis of the hepatic veins, frequently present during the course of cirrhosis and rare in thrombosis of the portal vein except in the presence of ascites. Determinations of the urobilin content of the urine are not helpful in making a differentiation, as excess amounts may occur in uncomplicated polycythaemia vera,⁴¹ cirrhosis¹¹ and thrombosis of the hepatic veins.

The plasma cholesterol partition was particularly striking in 1 case (case 60), indicating the profound degree of hepatic damage that might be expected in thrombosis of the hepatic veins.

Thus it is evident that simple, old thrombosis of the portal vein is often a relatively benign complication of polycythaemia vera, although it carries with it the threat of ultimate mesenteric thrombosis and intestinal gangrene. The condition may last for many years and produce

TABLE 5—*Incidence of Hepatic Enlargement, Ascites and Jaundice in Polycythaemia Vera Complicated by Thrombosis of Portal Vein, Thrombosis of Hepatic Veins and Hepatic Cirrhosis*

	Thrombosis of Portal Vein (14 Cases)	Hepatic Cirrhosis (10 Cases)	Thrombosis of Hepatic Veins (7 Cases)
Hepatic enlargement	5 cases ¹	7 cases	6 cases ²
Decrease under observation	1 case ³	2 cases	1 case ³
Ascites	4 cases ⁴	4 cases	7 cases
Effectiveness of mercurial diuretics	+	+	0
Jaundice	3 cases	7 cases	6 cases

1 Thrombosis of hepatic veins present in 2 of these cases. In another case the liver was of normal size at autopsy.

2 Atrophic cirrhosis was present in the 1 case in which hepatic enlargement was lacking.

3 Early cirrhosis (secondary to thrombosis of the hepatic veins) was present in this case.

4 Thrombosis of the hepatic veins was present in 2 of these cases.

few, if any, clinical manifestations. On the other hand, when a patient with polycythaemia vera presents an enlarged liver and ascites of non-cardiac origin, the diagnosis is, in all probability, complicating hepatic cirrhosis or thrombosis of the hepatic veins or both rather than thrombosis of the portal vein. On the basis of statistical frequency, cirrhosis is the more likely diagnosis, especially if the ascites has accumulated slowly and has responded to mercurial diuretics and if the liver is observed to decrease gradually in size. However, thrombosis of the hepatic veins is an almost certain diagnosis in the presence of sudden enlargement of the liver, rapid accumulation of ascites, resistance of the ascites to mercurial diuretics, terminal jaundice and a markedly abnormal plasma cholesterol partition.

SUMMARY

A case of polycythaemia vera is reported in which the appearance of sudden hepatic enlargement, rapid development of ascites and jaundice were found to be due to thrombosis of the hepatic veins.

41 Weber, F. P. Polycythemia, Erythrocytosis and Erythremia (Vaquez-Osler Syndrome), London, H. K. Lewis & Co., 1921.

The incidence and significance of enlargement of the liver in 60 cases of polycythaemia vera are discussed. In half the cases hepatic enlargement was moderate or marked. Marked enlargement of the liver often signifies the presence of a complication, such as phenylhydrazine jaundice, leukemic transformation, myocardial decompensation, hepatic cirrhosis or thrombosis of the hepatic veins.

In order to facilitate the clinical diagnosis in cases of polycythaemia vera associated with hepatic enlargement, ascites and jaundice, the literature was searched for instances of hepatic cirrhosis and thrombosis of the hepatic and portal veins complicating this disease. Study of the collected reports of cases discloses such points of diagnostic usefulness as sudden enlargement of the liver, rapid accumulation of ascites, resistance of ascites to mercurial diuretics, frequent terminal jaundice and a markedly abnormal plasma cholesterol partition in thrombosis of the hepatic veins, occasional decrease in the size of the enlarged liver and the effectiveness of diuretic measures in the ascites of cirrhosis, and the infrequency of ascites, hepatic enlargement and jaundice in thrombosis of the portal vein.

Dr B S Oppenheimer gave me permission to include the data for a large number of patients from his service.

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BLOOD "GUANIDINE" IN ARTERIAL HYPERTENSION

A REVIEW OF EIGHT HUNDRED CASES

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Since the initial publication in 1927 by Weber and myself,¹ describing an increase in the "guanidine" content of the blood of certain patients with arterial hypertension, a fairly extensive literature has grown up on this subject. In our first publication¹ we submitted data on 21 patients with hypertension, pointing out at that time that 7 of these patients, with an increase in the "guanidine" content of the blood, showed nitrogen retention, that 11 patients showed no nitrogen retention and that 3 patients showed no increase in the "guanidine" content. In a further report published in the same year² readings were presented for 35 patients who showed no nitrogen retention and for 5 patients who showed nitrogen retention. Twelve patients with arterial hypertension showed no increase in the "guanidine" content of the blood. One patient with arterial hypertension and nitrogen retention showed no increase in the "guanidine" content.

These results have been confirmed by some and questioned by others. Piffner and Myers³ found that the "guanidine" content was elevated in certain cases of hypertension. De Wesselow and Griffiths⁴ found an increase in ten of twenty-three estimations. On the other hand, Turriès and Robert⁵ stated that the "guanidine" estimations have been of no value from either diagnostic or prognostic standpoints, although they presented no records of estimations. Kleeberg and Schlapp⁶ found

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1 Major, R. H., and Weber, C. J. The Probable Presence of Increased Amounts of Guanidine in the Blood of Patients with Arterial Hypertension, *Bull. Johns Hopkins Hosp.* **40**: 85 (Feb.) 1927.

2 Major, R. H., and Weber, C. J. The Possible Increase of Guanidine in the Blood of Certain Persons with Hypertension, *Arch. Int. Med.* **40**: 891 (Dec.) 1927.

3 Piffner, J. J., and Myers, V. C. On the Colorimetric Estimation of Guanidine Bases in Blood, *J. Biol. Chem.* **87**: 345 (June) 1930.

4 De Wesselow, O. L. V., and Griffiths, W. J. The Blood Guanidine in Hypertension, *Brit. J. Exper. Path.* **13**: 428 (Oct.) 1932.

5 Turriès, J., and Robert, S. Recherches cliniques sur la guanidine du sang (en dehors de la tétanie), *Presse méd.* **38**: 85 (Jan. 18) 1930.

6 Kleeberg, J., and Schlapp, W. Ueber die Auffindung von uraemieerzeugenden Stoffen, *Ztschr. f. physiol. Chem.* **188**: 81, 1930.

an increase in the "guanidine" content in certain patients with arterial hypertension, while others showed no such increase. They found, as we did, that the high "guanidine" values were obtained for patients with nitrogen retention. Bohn and Schlapp⁷ concluded "In pale hypertension an increase in the guanidine values of the blood was found in the overwhelming majority of the cases studied. In red hypertension the guanidine values fall in the normal limits." Weiss⁸ stated that Jackson, in a personal communication, had informed him that he had been unable to establish any correlation between hypertension and the "guanidine" content of the blood.

We have recently completed a chemical study of the blood of 800 patients with arterial hypertension observed during the past ten years. The method employed for the estimation of the "guanidine" content was the original "method of Major and Weber," which was described in 1927, and the determinations were all made by 3 persons who were familiar with the procedure. We have found from experience that most beginners obtain results that are too high, and it is only after a certain amount of experience has been gained that the determinations become reliable.

In studying these patients we have placed them in groups based on the content of nonprotein nitrogen in the blood. Determinations of creatine, creatinine and uric acid were also made simultaneously, but the nonprotein nitrogen values were employed as the best indication of nitrogen retention. The accompanying table summarizes the results.

In our experience with our own method the normal "guanidine" value does not exceed 0.2 mg., and in the great majority of persons it varies between 0.1 and 0.15 mg. Patients showing a "guanidine" content above 0.2 mg. have been classed as having an increased content.

From a survey of the accompanying table it is seen that of 625 patients having hypertension and a nonprotein nitrogen content of 40 mg. or less, 200 showed an increased content of "guanidine" while 425 showed no increase. As the values for nonprotein nitrogen rose, the percentage showing an increase in the "guanidine" content also rose. Summarizing these results, 43 per cent of the entire series showed an increase in the "guanidine" content of the blood, while 32 per cent of those whose blood had a nonprotein nitrogen content not exceeding 40 mg. per hundred cubic centimeters showed an increase.

Further investigation of the color reaction has increased our suspicion that we are actually dealing with a guanidine derivative. Until it is,

7 Bohn, H., and Schlapp, W. Der Guanidingehalt des Blutes beim blassen und roten Hochdruck, *Zentralbl. f. inn. Med.* 53:571, 1932.

8 Weiss, S. The Etiology of Arterial Hypertension, *Ann. Int. Med.* 8:296 (Sept.) 1934.

however, definitely identified, we shall continue to use the term guanidine in quotation marks

The fact that some of the guanidine compounds are strongly pressor has excited much interest in connection with the thought that guanidine may be concerned in the mechanism of hypertension. However, in 1929, it was pointed out that while guanidine and methylguanidine are active pressor compounds, certain other guanidine compounds are depressor and still others are inert as far as their effect on the blood pressure is concerned.⁹ The compound which we have been studying, as we have

Summary of Results

Nonprotein Nitrogen Mg per 100 Cc	No of Cases	
	Increase in "Guanidine" Content	No Increase in "Guanidine" Content
40 or under	200	425
41-45	18	13
46-50	14	2
51-55	13	7
56-60	4	3
61-65	2	1
66-70	7	2
71-75	4	2
76-80	9	2
81-85	6	1
86-90	8	1
91-95	5	0
96-100	6	0
100	45	0
	<hr/> 341	<hr/> 459

mentioned on previous occasions, may prove to be a depressor or an inert substance when it is finally identified and its pharmacologic properties are studied. It is of some interest to note that the percentage of increased "guanidine" values for the hypertensive patients in this series of 800 patients is approximately the same as that obtained a number of years ago for a smaller group.

Our investigation of the blood in hypertension over a period of ten years has convinced us that our first statement made on this subject, in 1927, is still valid that "the blood of certain patients suffering from arterial hypertension contains something which is present in greater amounts than in normal blood."

⁹ Major, R. H. Observations on the Effects of Certain Guanidine Compounds upon the Blood Pressure, *Tr. A. Am. Physicians* **44**: 332, 1929.

CLINICAL ASPECTS OF ANEURYSM

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Aneurysms have been recognized and treated since the time of Galen, in the second century. The articles that were written on this subject before 1800 were collected by Erichsen¹ for the Sydenham Society. Klotz,² in 1926, reviewed the general subject of aneurysm completely, and Fearnside³ reviewed the history of intracranial aneurysm thoroughly. Those who are interested in the early history of this subject should consult these sources.

MATERIAL

The material for the present study included all the cases in which a diagnosis of aneurysm was seriously considered at the Mayo Clinic in the years 1925 to 1935, inclusive, except those in which there was an arteriovenous aneurysm or an aneurysm of the chambers of the heart.

In this series of 596 cases the aneurysms have been divided roughly into five anatomic groups (fig. 1): intracranial aneurysms, intrathoracic aneurysms (including those of intrathoracic vessels other than the aorta), intra-abdominal aneurysms (including those of intra-abdominal vessels other than the aorta), aneurysms of the extremities and a group of miscellaneous aneurysms. In the great majority of cases ample opportunity for complete clinical and laboratory studies was at hand to facilitate the diagnosis. The diagnosis with respect to 40, or 28 per cent, of the 143 intracranial aneurysms, 50, or 14.7 per cent, of the 339 thoracic aneurysms, 65, or 81.3 per cent, of the 80 intra-abdominal aneurysms, 8, or 38 per cent, of the 21 aneurysms of the extremities, and 9, or 69.2 per cent, of the 13 miscellaneous aneurysms, was verified by operation or necropsy. For a total of 172, or 28.9 per cent, of the 596 cases of aneurysm in this series, the diagnosis was verified by operation or necropsy.

The incidence of syphilis in this series of cases is shown in figure 2. Only 6 of the patients were Negroes, but all 6 of them had syphilis. Five of them had a thoracic aneurysm, and the sixth one had an abdominal aneurysm.

From the Division of Medicine, the Mayo Clinic.

1 Erichsen, J. N. Observations on Aneurysm, London, The Sydenham Society, 1844.

2 Klotz, O. Concerning Aneurysms, Toronto, University of Toronto Press, 1926.

3 Fearnside, E. G. Intracranial Aneurysms, Brain **39**: 224-296, 1916.

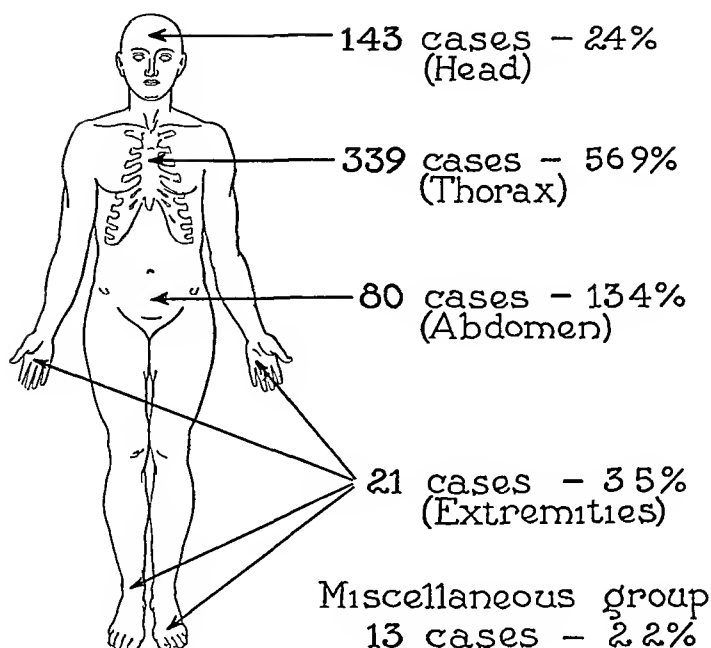


Fig 1—Anatomic distribution of the aneurysms observed in 596 patients at the clinic from 1925 to 1935, inclusive

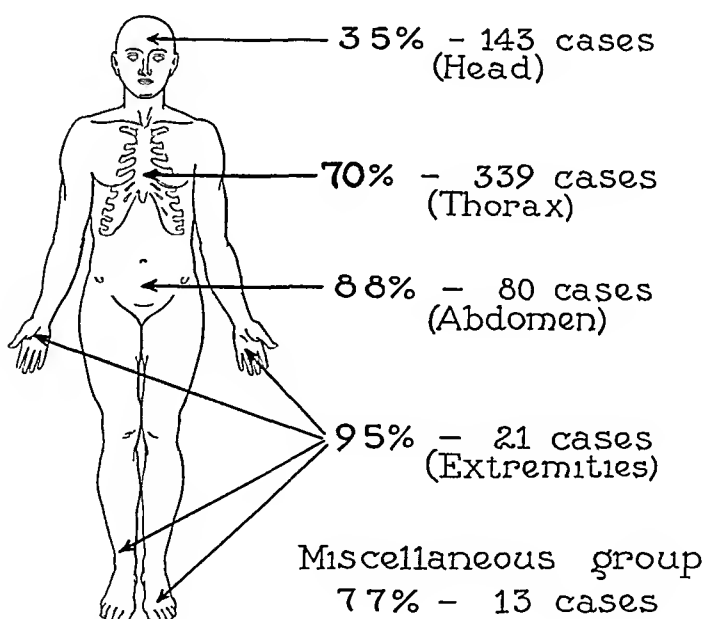


Fig 2—Incidence of syphilis in 596 cases of aneurysm

INTRACRANIAL ANEURYSM

In order to facilitate an analysis of the cases of intracranial aneurysm, the cases have been divided into two groups. Group 1 includes the 40 cases in which the presence of an aneurysm was verified at operation or necropsy, and group 2 includes the 103 cases in which the diagnosis was based on the clinical data.

Etiology—Tuffnell,⁴ in 1853, drew attention to the probability that embolism is the starting point of cerebral aneurysm. Lebert,⁵ in 1866, expressed the opinion that syphilis and alcohol are not definite causes of this lesion. In 6 of the 13 cases reported by Church,⁶ the aneurysm was thought to be the result of embolism, and characteristic vegetations were observed on the cardiac valves.

Eppinger,⁷ in 1887, first proposed that an intracranial aneurysm arises as the result of a congenital defect in the muscular wall of the arteries. Weber and Bode,⁸ suggested that the tendency of several congenital defects to occur in the same patient is also a factor in the frequency of aneurysm in association with coarctation of the aorta. Strauss, Globus and Ginsburg,⁹ stated the opinion that arteriosclerosis is the most important cause of intracranial aneurysm.

There was a history or evidence of syphilis in 3, or 7.5 per cent, of the cases in group 1 (table 1), but a history or evidence of syphilis was present in only 2, or 1.9 per cent, of the cases in group 2 (table 2). Therefore, evidence of syphilis was encountered in 5, or 3.5 per cent, of the 143 cases of intracranial aneurysm. This figure closely approximates the incidence of syphilis in the population at large.

The systolic blood pressure was more than 150 mm of mercury in 14, or 35 per cent, of the cases in group 1. A significant degree of arteriosclerosis of the peripheral vessels was noted in 5, or 12.5 per cent, of the cases in this group. This suggests that high blood pressure

4 Tuffnell, cited by Homes, T. Aneurism of the Internal Carotid Artery in the Cavernous Sinus, *Tr. Path. Soc. London* **12** 61-63, 1860-1861.

5 Lebert, H. Ueber die Aneurysmen der Hirnarterien, *Berl. klin. Wchnschr.* **3** 209-212 (May 14), 229-231 (May 28), 249-251 (June 11), 281-285 (July 9), 336-338 (Aug. 20), 345-347 (Aug. 27), 386-390 (Oct. 1), 402-405 (Oct. 15) 1866.

6 Church, W. S. On the Formation of Aneurysms, and Especially Intracranial Aneurysms in Early Life, *St. Barth. Hosp. Rep.* **6** 99-112, 1870.

7 Eppinger, H. Pathogenesis (Histogenesis und Aetiologie) der Aneurysmen einschliesslich des Aneurysma equi vermineum, *Arch. f. klin. Chir. (suppl.)* **35** 1-563, 1887.

8 Weber, F. P., and Bode, O. B. Congenital and Developmental Aneurysms, and Their Importance in Regard to the Occurrence of Sudden Intracranial (Especially Subarachnoid) Haemorrhage, *Internat. Clin.* **2** 1-14, 1929.

9 Strauss, I., Globus, J. H., and Ginsburg, S. W. Spontaneous Subarachnoid Hemorrhage. Its Relation to Aneurysms of Cerebral Blood Vessels, *Arch. Neurol. & Psychiat.* **27** 1080-1132 (May) 1932.

is of some importance in the development of an intracranial aneurysm, but it may be that the elevation of the blood pressure merely favors the development of aneurysmal pouchings in a vessel that has been abnormally weak since birth because of defects in the muscular walls. This has been suggested by Forbus¹⁰

TABLE 1—*Situation of Aneurysm, Age and Sex of Patients and Incidence of Syphilis in Forty Cases (Group 1) in Which the Diagnosis of Intracranial Aneurysm Was Verified*

Site of Aneurysm	No of Cases	Sex		Age, Years					Evidence of Syphilis		
		Males	Fe males	21 to 30	31 to 40	41 to 50	51+		Posi tive	Nega tive	Ques tion able
Circle of Willis	8	6	2	1	1	2	4			8	
Middle cerebral artery	10	5	5		3	3	4			10	
Anterior cerebral artery	5	3	2	1	1	1	2	1	1	4	
Posterior cerebral artery	2	1	1			1	1	1	1	1	
Internal carotid artery	8	5	3	1		2	5			7	1
Basilar artery	3	2	1		1	1	1			3	
Vertebral artery	3	2	1				3	1	1	2	
Not specified	1	1					1			1	
Total	40	25	15	3	6	10	21	3	36	1	
Percentage		62.5	37.5	7.5	15	25	52.5	7.5	90	2.5	

TABLE 2—*Site of Aneurysm, Age and Sex of Patients and Incidence of Syphilis in One Hundred and Three Cases (Group 2) in Which the Diagnosis of Intracranial Aneurysm Was Based on the History and Clinical Data*

Site of Aneurysm	No of Cases	Sex		Age, Years					Evidence of Syphilis	
		Males	Fe males	11 to 20	21 to 30	31 to 40	41 to 50	51+	Posi tive	Nega tive
Circle of Willis	34	14	20	2	6	7	8	11		34
Left cerebral artery	3	1	2	2				1		3
Right cerebral artery	4	1	3	1				3		4
Middle cerebral artery	7	3	4	1		2		4		7
Anterior cerebral artery	1	1			1					1
Internal carotid artery	7	4	3		1	2	1	3		7
Basilar artery	8	5	3	1	1	3	2	1		8
Vertebral artery	2	2		1				1		2
Sigmoid sinus	1	1		1						1
Cavernous sinus	3	1	2			1	1	1		3
Not specified	33	20	13	2	2	5	13	11	2	31
Total	103	53	50	11	11	20	25	36	2	101
Percentage		51.5	48.5	10.7	10.7	19.4	24.3	34.9	1.9	98.1

Trauma was considered a possible etiologic factor in only 4 of the 143 cases of intracranial aneurysm. In 1 of the 4 cases the presence of the aneurysm was verified. In 1 case in which the diagnosis was verified the aneurysm was the result of trauma which occurred in the course of an operation for severe mastoiditis.

¹⁰ Forbus, W. D. Ueber den Ursprung gewisser Aneurysmen der basalen Hirnarterien, *Centralbl f allg Path u path Anat* 44:243-245 (Jan 20) 1929.

It is extremely interesting that in this series of cases there was no evidence of bacterial endocarditis, which was an etiologic agent in such a high percentage of the cases reported by earlier authors¹¹ Bacterial endocarditis occurs rather commonly among the patients seen at the clinic, approximately 200 cases were noted in the period in which these cases of aneurysm were noted However, only a small percentage of the patients who had endocarditis remained at the clinic after the diagnosis was established, and although some of them may have died of rupture of a mycotic aneurysm, it is not possible to include them in this series

Although authors do not agree on the relative incidence of intracranial aneurysm in the two sexes, this type of aneurysm appears to occur slightly more often in males Intracranial aneurysm occurs at all ages It is relatively more frequent in young persons than are aneurysms that are situated in other parts of the body

Incidence—Fea insides³ encountered 51 intracranial aneurysms, 191 aneurysms of the aorta, 43 aneurysms of other large arteries and 44 aneurysms of small arteries other than cerebral vessels in 5,432 cases in which necropsy was performed

Situation—The peculiar predilection of intracranial aneurysm to involve the vessels at the base of the brain, within a short distance of the point at which they enter the cranial cavity or at the points of bifurcation, is a feature of such constancy as to be of important diagnostic significance

Most authors say that the middle cerebral artery is the vessel that is most commonly involved and that the basilar artery is involved next in order of frequency There is doubtless a relation between the frequency of aneurysm of the middle cerebral artery and the fact that this vessel and its branches are most prone to hemorrhage (Wechsler¹²) The site of the aneurysms in this series of cases is shown in tables 1 and 2

Symptoms—In this series of cases the situation of the pain in the head did not seem to be of much value in localizing the site of the aneurysm This is contrary to the opinion of Gowers¹³ and that of Fea insides,³ as these authors expressed the opinion that occipital pain is the predominating symptom in cases of aneurysm of the basilar artery

11 Tuffnell⁴ Eppinger⁷

12 Wechsler, I S A Textbook of Clinical Neurology, ed 3, Philadelphia, W B Saunders Company, 1931

13 Gowers, W R Intracranial Aneurism, in A Manual of Diseases of the Nervous System, Philadelphia, P Blakiston, Son & Co, 1888 pp 907-917

Pain in the back and legs is significant when it occurs with other signs or symptoms of intracranial hemorrhage, as it is an indication of irritation of the posterior roots of the spinal nerves by free blood in the spinal canal. Fearnside¹⁴ said that stiffness of the neck is of definite localizing value, as it is an indication of hemorrhage from one of the posterior group of vessels. In the present series this symptom did not occur in any case in which the presence of an aneurysm of one of the posterior group of vessels was suspected or verified. In this series, attacks of grand mal occurred more often in cases in which the aneurysm involved the anterior vessels than they did in cases in which the posterior group of vessels was involved. The frequency with which this symptom occurred is of interest in view of the fact that it was thought to occur most often in cases in which an embolic aneurysm was situated near the cortical or subcortical area. This series did not include any case of mycotic aneurysm. One or more attacks of unconsciousness were second only to pain as the most frequent symptom.

The duration of symptoms of intracranial aneurysm varied from a few hours to thirty-five years, the average duration being twenty-six months.

Repeated seizures, which are caused by intermittent leakage from the aneurysm, have always been an important diagnostic point in cases of intracranial aneurysm. Such attacks occurred in 7, or 17.5 per cent, of the cases in group 1 and in 29, or 28.2 per cent, of the cases in group 2. In the latter group of cases these attacks often were the deciding factor in establishing the diagnosis.

In the cases in group 1, signs of pyramidal involvement were more frequently associated with aneurysm of the anterior group of intracranial vessels than they were with aneurysm of the posterior group of vessels. Peripheral sensory disturbances were present in 20 per cent of the cases in this group. Nystagmus occurred more frequently in association with aneurysm of the posterior group of vessels than it did in association with aneurysm of the anterior group. Parker¹⁴ expressed the opinion that disturbances of speech are symptoms peculiar to aneurysm of the posterior group of intracranial vessels. However, in this series, disturbances of speech occurred not only in cases in which the posterior group of vessels was involved but also in 3 cases in which the anterior group was involved. Bruit, although admittedly a rare symptom of intracranial aneurysm, occurred in 2 cases in group 1 and in 1 case in group 2. When paralysis of the cranial nerves occurred in group 1, the oculomotor nerve was involved most frequently. This has been noted in other cases reported in the literature. The hypoglossal nerve was involved next in frequency, but this probably was a

¹⁴ Parker, H. L. Aneurysms of Cerebral Vessels. Clinical Manifestations and Pathology, *Arch Neurol & Psychiat* **16** 728-746 (Dec.) 1926.

chance occurrence. In the cases in group 2 the oculomotor nerve was involved most frequently, and involvement of the facial and abducens nerves was next in order of frequency.

Dysphagia, anosmia and disturbances of taste each occurred in 1 case in group 1, and deafness occurred in 2 cases in group 1.

The blood pressure was elevated in 14, or 35 per cent, of the cases in group 1 and in 24, or 23.3 per cent, of the cases in group 2. Peripheral arteriosclerosis was mentioned in only 5 of the cases in group 1 and in only 11 of the cases in group 2. While these figures are not sufficiently conclusive, they suggest that arteriosclerosis and hypertension play a role in the production of intracranial aneurysm.

In 8 cases in group 1 there were no objective symptoms of aneurysm. In 2 of these cases the aneurysm was an incidental observation at necropsy and could not have been responsible for the symptoms.

In 4 cases in group 1 there were no physical findings that suggested the presence of an intracranial aneurysm, but the past history was so suggestive that the diagnosis was seriously entertained, in spite of the absence of clinical findings.

Laboratory and Special Findings—The presence of xanthochromic or bloody fluid within the spinal canal is of great weight in establishing the diagnosis. Xanthochromic cerebrospinal fluid was found in 5 and bloody spinal fluid in 11 of the cases in group 1. The pressure of the cerebrospinal fluid was increased in 2 cases. The number of patients subjected to this diagnostic procedure was substantially less than the total number of cases. Bloody spinal fluid was present in 13, xanthochromic cerebrospinal fluid was present in 15 and the pressure of the fluid was increased in 1 of the cases in group 2. Examination of the cerebrospinal fluid in the interim between attacks cannot be expected to yield a high percentage of positive findings.

Choked disks occurred in 5, or 12.5 per cent, defects in the visual fields were mentioned in 4, or 10 per cent, and retinal hemorrhage and atrophy of the optic nerve were each observed in 1 case in group 1, while choked disks were found in 9, or 8.7 per cent, visual defects occurred in 18, or 17.5 per cent, and retinal hemorrhages occurred in 4, or 3.9 per cent, of the cases in group 2. The defects in the visual fields ranged from small ones to total blindness. Atrophy of the optic nerve was observed but once in group 1. The presence of choked disks is interesting in view of the fact that there was manometric evidence of increased pressure in only 2 cases in group 1 and in only 1 case in group 2. This suggests that the papilledema was not the result of a general change in the pressure of the cerebrospinal fluid. It likely was a local disturbance in the optic nerve, which probably was the result of hemorrhage within the nerve sheath or possibly was caused by the pressure of the aneurysm.

Roentgenologic examination has been of some aid in the diagnosis of intracranial aneurysm. Calcification has been demonstrated in the walls of an aneurysm. This is often misinterpreted, however, because of the similarity in the appearance of calcification in the walls of an aneurysm or within an aneurysmal sac and the calcification which often occurs in an intracranial cyst or tumor. Aneurysm at times produces unilateral erosion of the anterior or posterior clinoid processes. When the hemorrhage is large and occurs into the substance of the brain, actual displacement of the ventricles may take place, as was observed in 1 of the cases in group 1, or a shift of a calcified pineal body may be observed, as it was in 1 of the cases in group 2.

The ability to diagnose intracranial aneurysm during life has undergone a change in recent years. In the first ten editions of Osler's "Textbook of Medicine," the concluding paragraph in the section dealing with intracranial aneurysm contained the statement that "diagnosis is, as a rule, impossible." However, in the eleventh edition, this statement was altered to read "The diagnosis should be made if its possibility is considered."

Mode of Termination—In cases in which an intracranial aneurysm produces symptoms, the most frequent cause of death is rupture of the aneurysm. In all the cases reported by Wichern,¹⁵ the patient died of rupture of the aneurysm. In the present series, rupture of the aneurysm occurred in 28 per cent of the cases. In many cases the patient was lost from view, or the records were incomplete, therefore, this figure is unquestionably low.

Differential Diagnosis—In the differential diagnosis in the cases in group 1, tumor of the brain was seriously considered in 12, or 30 per cent, encephalitis was considered in 3, or 7.5 per cent, and cerebral hemorrhage was considered in 3, or 7.5 per cent. An inflammatory condition, its nature not being further specified, was considered in 2, or 5 per cent, of the cases, and tuberculous meningitis was considered in 2, or 5 per cent, of the cases.

A metastatic malignant growth, thrombosis of the posterior inferior cerebellar artery, angioma and syphilitic meningitis were each considered in the differential diagnosis in 1 instance.

In the cases in group 2, tumor of the brain was considered in 31, or 30.1 per cent, encephalitis was considered in 9, or 8.7 per cent, and cerebral hemorrhage unrelated to aneurysm was considered in 11, or 10.7 per cent. The diagnosis of migraine entered into consideration in the differential diagnosis in 7, or 6.8 per cent, of the cases.

In 3 cases hysteria also was considered, and tuberculous and syphilitic meningitis each were considered in 1 case. Thrombosis

¹⁵ Wichern, H. Klinische Beiträge zur Kenntnis der Hirnaneurysmen, Deutsche Ztschr. f. Nervenhe. **44** 220-263 (May) 1912.

(basilar artery), in addition to cerebral aneurysm, was considered in 2 cases. In 4 cases the clinical picture was sufficiently typical to cause the clinicians to entertain a diagnosis of intracranial aneurysm, but necropsy disclosed a tumor. In 1 case the appearance of the mass, as seen at operation, justified a diagnosis of intracranial aneurysm, but necropsy proved that the growth was a neoplasm. In 1 case, although the symptoms were characteristic of intracranial aneurysm, necropsy revealed only evidence of an inflammatory lesion of undetermined nature at the base of the brain. Metastases of an unsuspected hypernephroma was responsible for the symptoms in 1 case in which the diagnosis of intracranial aneurysm was considered.

THORACIC ANEURYSM

Etiology—Since the earliest observations, the relation between syphilis and aneurysm of the aorta has been noted, approximately 85 per cent of these lesions are said to develop on the basis of syphilitic aortitis. Most of the remaining aneurysms of the thoracic aorta are produced by arteriosclerosis.

In the present series of cases of thoracic aneurysm, approximately 70 per cent of the patients had syphilis. In 30 per cent of the cases there was no history of syphilis or evidence of the disease. In 18 per cent of the latter group of cases, arteriosclerosis of the higher grades (3 and 4) was present, but this association does not permit the assumption of the etiologic role of arteriosclerosis without anatomic confirmation. In 1 case bacterial endocarditis was responsible for an aortic aneurysm.

In the 339 cases of thoracic aneurysm in this series, 272 of the patients were males and 67 were females, therefore, the ratio of males to females was approximately 4:1 (table 3). This agrees rather closely with the ratio reported by other authors.

The rather advanced age of the patients in this series of cases may be attributable to the relatively low incidence of syphilis, as compared with that reported in other series of cases. This seems to indicate that arteriosclerosis, which occurs in the later years of life, probably was an etiologic factor in a large number of cases in this series.

Symptoms—Pain, dyspnea, cough and hoarseness were the most frequent symptoms in the cases of thoracic aneurysm. The thoracic pain was limited to the left side in 66, or 19.5 per cent, of the cases and was confined to the right side in 40, or 11.8 per cent, of the cases. Pre-cordial pain occurred in 36, or 10.6 per cent, of the cases, and sub-sternal pain was present in 25, or 7.4 per cent, of the cases.

Thoracic pain occurred in 33.3 per cent of the cases of aneurysm of the ascending aorta, in 68.7 per cent of the cases in which the aneurysm involved the ascending aorta and aortic arch, in 48.7 per cent of the

cases of aneurysm of the arch of the aorta, in 55.6 per cent of the cases in which the aneurysm involved the aortic arch and the descending aorta, in 42.2 per cent of the cases of aneurysm of the descending aorta, in 60 per cent of the cases in which the aneurysm was diffuse, in 25 per cent of the cases of aneurysm of the innominate artery, in 13.3 per cent of the cases of aneurysm of the common carotid artery and in 21.7 per cent of the cases in which there were multiple aneurysms. Pain was not present in any of the cases of aneurysm of the subclavian artery.

Eighty-eight, or 26 per cent, of the patients complained of pain in the shoulder. This pain was slightly more common in the left shoulder than it was in the right shoulder. In 46, or 13.6 per cent, of the cases

TABLE 3—*Site of Aneurysm and Age and Sex of Three Hundred and Thirty-Nine Patients with Intrathoracic Aneurysm*

Site of Aneurysm	No. of Cases	Sex		Age, Years				
		Males	Fe. males	11 to 20	21 to 30	31 to 40	41 to 50	51+
Ascending aorta	15	15				2	3	10
Ascending aorta and aortic arch	16	14	2			4	4	8
Arch of aorta	90	76	14		1	15	28	46
Aortic arch and descending aorta	27	24	3			1	7	19
Descending aorta	45	38	7	1		3	9	32
Diffuse in thorax	15	12	3			1	5	9
Innominate artery	8	3	5			1	1	6
Carotid artery	15	5	10			2	2	11
Subclavian artery	13	7	6			2	3	8
Multiple aneurysms in upper part of thorax	6	4	2			1	1	4
Not specified	89	74	15		2	13	32	42
Total	339	272	67	1	3	45	95	195
Percentage		80.2	19.8	0.3	0.9	13.3	28	57.5

the pain extended to the arm. There was pain in the back in 36, or 10.6 per cent, of the cases, and pain in the neck occurred in 33, or 6.8 per cent, of the cases.

In 28, or 8.3 per cent, of the cases data were not available as to the situation of the pain.

The pain produced by aneurysm was often stated to be aggravated by exercise, recumbency, coughing, deep breathing and changes in the weather. The pain that is produced by exercise is often true angina pectoris that is associated with the intimal overgrowth at the orifices of the coronary vessels. In other instances the exacerbation of pain by exertion may be the result of an increase in the size of the aneurysmal sac. Boyd¹⁶ said that next to pain dyspnea is the most frequent symptom of intrathoracic aneurysm. Dyspnea occurred in 39.5 per cent of the 339 cases. Cough occurred in 94, or 27.7 per cent, of the

¹⁶ Boyd, L. J. A Study of Four Thousand Reported Cases of Aneurysm of Thoracic Aorta, *Am J M Sc* **168** 654-660 (Nov) 1924.

cases In 73, or 21.5 per cent, of the cases a visible pulsation or mass was detected by the patient Hoarseness was a common symptom, it occurred in 58, or 17.1 per cent, of the cases Hemoptysis was present in 25, or 7.4 per cent, of the cases, this varied from blood-streaked sputum to frank pulmonary hemorrhage, in which several ounces of blood was expectorated Orthopnea was present in 16, or 4.7 per cent, of the cases, and 10, or 2.9 per cent, of the patients complained of edema Palpitation was present in 30, or 8.8 per cent, of the cases, and a local area of tenderness over the aneurysm was present in 11, or 3.2 per cent, of the cases

Dysphagia was present in 4, or 1.2 per cent, and numbness of the arms was present in 7, or 2.4 per cent, of the cases About 10 per cent of the patients complained of extreme generalized weakness Fifty-three, or 14.6 per cent, of the patients did not have any symptoms referable to the cardiorespiratory system Cough, weakness, edema, palpitation and edema also are symptoms of syphilis of the cardiovascular system However, in the presence of syphilis and any of the important symptoms of syphilitic vascular involvement, concomitant aneurysm should be suspected

Abnormalities of the Cardiovascular System—The heart was enlarged in 103, or 30.4 per cent, of the cases of intrathoracic aneurysm In a great many cases the cardiac murmurs clearly indicated the presence of valvular defects which could account for the cardiac enlargement In addition, the rather high incidence of arteriosclerosis (18 per cent) and the relative frequency of a systolic blood pressure of more than 150 mm of mercury (in 96, or 28.3 per cent, of the cases) indicate that this factor also can contribute to the presence of cardiac enlargement Significant enlargement, grades 2 to 4, was present in only 10 per cent of the cases

Eighty-one patients, or 23.9 per cent, were suffering from various degrees of arteriosclerosis, grades 1 to 4, 19, or 5.6 per cent, had rather severe arteriosclerotic involvement (grade 3 or 4) This may be correlated with the observation that 57.5 per cent of the patients were 51 or more years of age and the incidence of syphilis was comparatively low (8.4 per cent)

The aortic second sound was accentuated in 48, or 14.2 per cent, of the cases

Systolic murmurs were present in 169, or 49.8 per cent, of the cases of intrathoracic aneurysm The systolic murmurs were best heard at the aortic area in 71 cases, at the apex in 52 cases and at the pulmonic area in 30 cases In 9 cases systolic murmurs were heard in all auscultatory areas, and in 7 cases the site of the murmur was not specified Diastolic murmurs were present in 69, or 20.4 per cent, of the cases The diastolic murmurs were best heard at the aortic area in 32 cases,

at the apex in 17 cases and at the pulmonic area in 10 cases. In 5 cases the murmur was heard in all the auscultatory areas, and in 5 other cases the site of maximal intensity of the murmur was not specified. Systolic and diastolic murmurs often were present in the same patient, but specific data regarding this point were not collected.

In 65 cases detectable differences in the pulse or blood pressure were elicited when the two arms were compared. Differences in the pulse are not as significant as differences in the blood pressure or a delayed pulse on one side. In 53, or 15.6 per cent, of the cases, no difference in the pulse or blood pressure could be elicited. In 3 of the cases of aneurysm of the subclavian artery a difference in the character of the pulse or blood pressure was noted, and in 4 cases definite efforts to reveal such differences were unsuccessful.

Physical Findings—In 97, or 28.6 per cent, of the cases of intra-thoracic aneurysm, either a pulsating or an expansile mass was observed. A palpable mass which was neither expansile nor pulsating was present in 49 cases. In 11 cases the mass was tender. A thrill was felt in the mass in 28 cases, and a bruit was present in the region of the aneurysm in 32 cases. Tracheal tug was present in 62 cases, and diastolic shock was mentioned in 17 cases.

Mediastinal widening was observed in 70 cases. There was evidence of bronchial occlusion in 18 cases. Seven patients had clubbed fingers. Cyanosis was present in 23 cases. The right vocal cord was fixed in 6 cases and the left vocal cord in 31 cases. An additional patient had paralysis of both vocal cords, but this was thought to be the result of syphilitic mediastinitis.⁹ Physical examination did not disclose any abnormality in 10 cases, in 4 of these cases there was an aneurysm of the descending aorta.

The average duration of symptoms before the diagnosis was made at the clinic was thirty-six months. The more remote the aneurysm was from the heart, the longer the symptoms had been present before a diagnosis was made. In 116 cases information was obtained regarding the length of life after the diagnosis was established. The diagnosis was confirmed at necropsy in 35 of these cases. In 81 cases the patient lived from a few hours to ten years after the diagnosis was made, the average duration of life after diagnosis being twenty and one-half months.

ABDOMINAL ANEURYSM

Of the patients with abdominal aneurysm, 68.7 per cent were males and 31.3 per cent were females. The abdominal aorta was involved in 32.5 per cent of the cases, and multiple aneurysms were present in 21.3 per cent of the cases. In 3 cases thoracic and abdominal aneurysms were both present. The incidence of syphilis was rather low, as evi-

dence of syphilis was obtained in only 8.8 per cent of the cases. In 86.2 per cent of the cases the patients were more than 51 years of age. This suggests the importance of arteriosclerosis as the etiologic agent in aneurysm in this region.

Thirty-two patients, or 40 per cent, had significant degrees of arteriosclerosis, and 21 patients, or 26.2 per cent, had a severe degree of arteriosclerosis (grade 3 or 4).

Bacterial endocarditis was the responsible factor in 2 cases of mycotic aneurysm, in 1 of these cases the splenic artery was involved and in the other the renal artery. In only 1 case did an aneurysm of the splenic artery produce symptoms, and in this case there were no symptoms until rupture of the mycotic aneurysm caused a fatal hemorrhage.

In 39, or 48.8 per cent of the cases there were no symptoms that were directly referable to the aneurysm. Symptoms of cardiovascular disease and generalized arteriosclerosis predominated. An abdominal mass was detected in 24, or 30 per cent, of the cases. The mass had been detected by the patient in 8, or 10 per cent, of the cases. The mass was observed to pulsate in 22, or 27.5 per cent, of the cases and was expansile in 5, or 6.3 per cent, of the cases. A bruit was present over the mass in 9, or 11.3 per cent, of the cases. Gastrointestinal symptoms were present in 7, or 8.8 per cent, of the cases.

Abdominal pain was present in 12 cases, in 1 case it was localized in the right upper quadrant of the abdomen and in 2 cases in the left lower quadrant. The systolic blood pressure was more than 150 mm. of mercury in 18, or 22.5 per cent, of the cases. Calcification was present in the wall of the aneurysm in 5, or 6.3 per cent, of the cases.

In 65, or 81.3 per cent, of the cases the diagnosis of aneurysm was verified by operation or necropsy.

ANEURYSM OF THE PERIPHERAL ARTERIES

In 21, or 3.5 per cent, of the entire series of cases the aneurysm involved the peripheral arteries of an extremity. Trauma was the cause of the aneurysm in 7 cases. Cases of congenital and acquired arteriovenous aneurysm have not been included in this group.

In the cases of aneurysm of the peripheral arteries the predominance of the male sex was evident, as it was in the cases in the other groups. Although the total number of cases is small, the significance of syphilis as an etiologic agent appears to be slight. Aneurysm of an extremity occurs earlier in life than aneurysm in other parts of the body, 38 per cent of the patients were less than 41 years of age.

Physical signs, for the most part, depend on the situation and the size of the aneurysm. No attempt is made in this paper to list these, as they are so well known.

Arteriosclerosis was present in 30 per cent of the cases. In 1 case of aneurysm of the femoral artery, bacterial endocarditis was present and may be considered the etiologic agent.

MISCELLANEOUS ANEURYSMS

This group included 13 cases. The following arteries were involved: an artery in the hypopharynx in 2 cases, an unspecified artery in the posterior cervical region in 1 case, an artery within the orbit in 2 cases, the ophthalmic artery in 1 case, an unnamed artery of the cheek in 1 case and a coronary artery in 6 cases. The aneurysm of the coronary artery was an incidental finding at necropsy in each case.

In 62 per cent of this group of cases the patients were males. A positive reaction to the Wassermann test of the serum was obtained in only 1 case (7.7 per cent); in this case there was an aneurysm of one of the coronary vessels. In this small group of cases, 69.2 per cent of the patients were more than 50 years of age. Four of the patients complained of a mass. A bruit was observed in 2 cases, a thrill was present in 3 cases and in 3 cases the mass was observed to pulsate. The systolic blood pressure was more than 150 mm. of mercury in 6, or 46 per cent, of the cases. An enlarged heart was found in 1 case, and severe arteriosclerosis (grade 3) was present in 2 cases. In 1 case of aneurysm of the orbit, erosion of the wall of the orbit was noted during roentgenologic examination.

Proptosis was present in both cases of aneurysm of the orbit. Loss of vision was present in 1 of these cases and also in the case of aneurysm of the ophthalmic artery. In 1 case aneurysm of the hypopharynx produced Horner's syndrome by pressure on the cervical sympathetic nerves.

SUMMARY

A total of 596 cases of aneurysm were recorded at the Mayo Clinic in the years 1925 to 1935, inclusive. In this series of cases, 143 of the aneurysms were intracranial, 339 were intra-thoracic, 80 were intra-abdominal, 21 involved the extremities and 13 were of a miscellaneous character. Syphilis was present in 3.5 per cent of the cases of intracranial aneurysm, in 70 per cent of the cases of thoracic aneurysm, in 88 per cent of the cases of intra-abdominal aneurysm, in 9.5 per cent of the cases of aneurysm of an extremity, and in 7.7 per cent of the miscellaneous cases of aneurysm. In a total of 172, or 28.9 per cent, of the 596 cases the diagnosis of aneurysm was verified at operation or necropsy.

ARTICULAR MANIFESTATIONS OF MENINGOCOCCIC INFECTIONS

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This presentation of cases and review of the literature were prompted by a case of meningococcic arthritis (the patient was seen at Bellevue Hospital during the aftermath of cerebrospinal meningitis) which went on to destroy several joints and produce ankylosis. This was contrary to my understanding of the prognosis in this condition. Preliminary investigation in the standard textbooks of medicine, including the various larger systems, revealed only cursory mention of this complication of epidemic meningitis.

Thus Herrick,¹ in Cecil's "Textbook of Medicine," said only that arthritis and arthralgias may occur and complicate the diagnosis in the early stages and that the prognosis is usually good. Leake,² in Tice's "Practice of Medicine," stated that the outcome of arthritis due to the meningococcus is not as serious as might be imagined and that there tends to be spontaneous and complete recovery. Rolleston and Andrewes,³ in Nelson's system of medicine, repeated this with a more complete discussion, similarly, Gordon,⁴ in the "Cyclopedia of Medicine," and Osler and McCrae⁵ in their textbook merely mentioned this condition and stated no prognosis. It was primarily to check the accuracy of this general concept that a review of all the cases that could be discovered was undertaken.

From the Orthopedic Service of Dr Krida, Bellevue Hospital, and the Orthopedic Service, Mount Sinai Hospital. The cases were taken from the Pediatric and the Third and the Fourth Medical Division of Bellevue Hospital and from the Pediatric, Medical and Neurologic services of Mount Sinai Hospital.

1 Herrick, W W. Cerebrospinal Fever, in Cecil, R L. A Textbook of Medicine, Philadelphia, W B Saunders Company, 1927, p 117.

2 Leake, J P. Meningitis, in Tice, F. Practice of Medicine, New York, W F Prior Company, 1920, vol 3.

3 Rolleston, H, and Andrewes, F W. Cerebrospinal Fever, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1926, vol 2, p 45.

4 Gordon, J E. Meningococcic Meningitis, in Piersol, G M, Bortz, E L, and others. Cyclopedia of Medicine, Philadelphia, F A Davis Company, 1933, vol 8, p 723.

5 Osler, W, and McCrae, T. Meningitis, in Principles and Practice of Medicine, ed 8, New York, D Appleton and Company, 1912, p 113.

This complication of cerebrospinal fever was recognized long before the discovery of the meningococcus in 1887 by Weichselbaum⁶. The earliest clinical mention was made by Welch,⁷ in 1810, and by North,⁸ in 1811, both of whom gave excellent, though brief, descriptions. Still,⁹ in 1898, and Gwyn,¹⁰ in 1899, first recovered the organism from the involved joint as well as from the blood and spinal fluid, and Osler¹¹ shortly afterward described the clinical characteristics in rather broad terms. Numerous reports on individual cases of meningococcic arthritis date back to 1856 in the French literature. These accounts extend up to the great epidemics which occurred just before, during and after the World War. Santon¹² listed at least a dozen papers, including the detailed reports of Netter and Deble, Comby and Sevestre, Netter and Durand, Lafosse, Maille and Santon (in several papers written with various co-authors).

The epidemics of cerebrospinal fever in military and naval encampments led to the excellent descriptions of the various manifestations of meningococcic infection by Rolleston,¹³ in England, and by Herrick¹⁴ and Parkhurst,¹⁵ in the United States, who described the largest group of cases of extrameningeal manifestations of meningococcic infection ever collected. In the last mentioned paper¹⁵ was given a more or less complete review of the literature up to 1919 on the articular complications of this disease.

Since 1919 the descriptions of this subject have been few and far between, consisting mainly of case reports. Weill, Dufourt and Bocca¹⁶ reported a fatal case in a 17 day old infant who had arthritis of the left knee and a cervical abscess, originating from the sternoclavicular joint, with no meningitis. Culture of the pus in the cervical abscess showed meningococci, which were also found in an abscess in the breast and in the nasopharynx of the mother. Jaffe¹⁷ gave details on case 4 of the present series (table 1). Kobayashi¹⁸ presented a 4 month old girl who

6 Park, W. H., Williams, A. W., and Krumwiede, C. *Pathogenic Microorganisms*, ed 9, Philadelphia, Lea & Febiger, 1929, p. 358.

7 Welch, T. *Dissertations of the Massachusetts Medical Society*, 1813, vol. 2, p. 135, cited by Osler¹¹.

8 North, E. *A Treatise on a Malignant Epidemic, Commonly Called Spotted Fever*, New York, T. & F. Swords, 1811, cited by Osler¹¹.

9 Still, G. F. *J. Path. & Bact.* **5**: 147, 1898.

10 Gwyn, N. B. *Bull. Johns Hopkins Hosp.* **10**: 112, 1899.

11 Osler, W. *Arthritis of Cerebrospinal Fever*, *Brit. M. J.* **1**: 1521, 1899.

12 Santon, P. *Lancet* **1**: 1080 (June 21) 1919.

13 Rolleston, H. *Lancet* **1**: 645 (April 19) 1919.

14 Herrick, W. W. (a) *Extrameningeal Meningococcus Infections*, *Arch. Int. Med.* **23**: 409 (April) 1919, (b) *Bull. New York Acad. Med.* **7**: 487 (July) 1931.

15 Herrick, W. W., and Parkhurst, G. M. *Am. J. M. Sc.* **158**: 473 (Oct.) 1919.

16 Weill, E., Dufourt, A., and Bocca. *Lyon med.* **130**: 504, 1921.

17 Jaffe, H. *J. Mt. Sinai Hosp.* **1**: 23 (May-June) 1934.

18 Kobayashi. *Orient. J. Dis. Infants* **16**: 22, 1934.

had the onset of diffuse arthritis of both feet, elbows, knees and hands, with swelling, fluctuation and formation of fluid, from which were cultured meningococci. There were no meningeal symptoms, and complete cure was obtained in three months. Campbell and Greenfield¹⁹ also presented a case of "cryptogenetic" arthritis of the knee of unknown etiology in a 15 month old boy. Culture of the fluid revealed meningococci, the outcome was not reported.

Several papers,²⁰ in addition, on so-called postmeningitic spondylitis, to be discussed presently, make up all that has been written on this subject since the World War except Herrick's^{14b} review, in 1931, of his experience during the war. Therefore, the scope of this paper was enlarged to include a general review of the entire subject and the presentation of 23 cases, many of them illustrating points in the clinical picture, diagnosis and prognosis of the condition previously scattered through the literature.

INCIDENCE

The reports of these cases (table 1) were selected from the records of Bellevue Hospital (17 cases), of Mount Sinai Hospital (4 cases) and of private physicians (2 cases), making 23 cases in all, records of the last ten years only were examined. It was impossible to estimate, from the various sources, the exact incidence of articular complications of meningococcic infection. All the patients had meningitis at some time during the course of the disease, some had clinical and bacteriologic meningococcemia. In the literature,²¹ the incidence of articular lesions is given as 4.8 to 20 per cent in various epidemics at different times.

In 6.5 per cent of Herrick's series¹⁵ of 902 cases of infection with meningococci there was articular involvement. Rolleston, in the British Navy epidemic, reported an incidence of 4.8 per cent, and Councilman, Mallory and Wright, cited by Herrick and Parkhurst,¹⁵ reported 5.4 per cent. Santon,¹² however, reported the incidence as being nearer 20 per cent. He emphasized the transiency in many of the cases, the dramatic nature of the meningitis and the extreme sickness of the patient, which made detailed examination of joints more difficult, causing the condition to be missed entirely in many cases. He said he believed the incidence to be much higher than is generally thought and that if carefully sought, infection of the joints is more often demonstrable. In a recent series of cases of epidemic meningitis in 169 children at Bellevue Hospital the incidence was 7.7 per cent.²²

19 Campbell, W., and Greenfield, E. C. *South African M. J.* **10** 545 (Aug. 8) 1936.

20 (a) Epstein, S. *Am. J. M. Sc.* **163** 401 (March) 1922, (b) *M. J. & Rec.* **128** 219 (Sept. 5) 1928. (c) Billington, R. W. *Spondylitis Following Cerebro-spinal Meningitis*, *J. A. M. A.* **83** 683 (Aug. 30) 1924.

21 Santon¹² Rolleston¹³

22 Bolduan, N. Personal communication to the author.

Infections of Joints

Duration of Serum Sickness	Other Complications	Treatment			Follow Up Period	Outcome	
		Specific	Orthopedic	Miscellaneous		Joints	General
		Serum, intra-spinal and intravenous		Dia-thermy	6 wk	Resolution	Cure
4-5 days	Iridocyclitis	Serum, intra-spinal and intravenous	Traction		2 mo	Resolution	Ocular defect
4-5 days	Encephalitis	Serum, intra-spinal and intravenous	Manipulation, drainage	Physical therapy	1 yr	Wrist cured, elbow and hip stiff	Residual encephalitis
	Syphilis, hepatitis and pneumonia	Serum, intra-spinal and intravenous	Wrist fluid, aspiration			Ankle cured, wrist better	Death due to pneumonia
		Serum, intra-spinal	Aspiration, splint	Physical therapy	1 yr	Slight limitation of flexion	Cured
3-4 days	Deafness	Serum, intra-spinal	Aspiration		2 yr	Resolution	Cured
2 wk	Strabismus and conjunctivitis	Serum, intra-spinal			1 mo	Resolution	Cured
?		Serum, intra-spinal				Resolution	Cured
'	Pregnancy	Serum, intra-spinal and intravenous			2 wk	Resolution	Death
		Serum, intra-spinal and intravenous				Resolution	Cure
?		Serum, intra-spinal				Resolution	Cure
3-4 days		Serum, intra-spinal	Casts	Physical therapy, fever therapy, blood transfusion		Ankylosis right elbow, wrist, carpometacarpal joints, partial ankylosis left elbow	Recovery
4-5 days		Serum, intra-spinal				Resolution	Cure
6-7 days		Serum, intra-spinal				Resolution	Cure
3-4 days	Deaf mute	Serum, intra-spinal	Aspiration and traction	Physical therapy	2 mo	Slight limitation of flexion	Recovery
6-7 days		Intraspinal, intravenous and into knee	Wrist and knee splints, aspiration	Physical therapy	3 mo	Slight residual general stiffness	Recovery
	Coma	Intraspinal and intravenous				Unchanged	Death, 6 days
3 days	Acute purulent otitis media	Intraspinal	Splint			Resolution	Cure
5 days		Intraspinal				Resolution	Cure
	Bilateral acute purulent otitis media	Intraspinal				Resolution	Cure
						Resolution	Cure

CLASSIFICATION

The present series of cases falls naturally into three major groups which are not sharply delineated. This corresponds with the classification given by Herrick and Parkhurst,¹⁵ the main characteristics are outlined in table 2 and will be discussed in detail.

Another classification depends on the occurrence of meningitis and the temporal relation of the arthritis to the meningeal symptoms, thus

I Meningococcic arthritis may be associated with epidemic meningitis

(a) It may occur from a few days to as long as two months before the meningitis, in polyarticular fashion, resembling rheumatic fever,

TABLE 2—*Meningococcic Arthritis (After Herrick and Parkhurst)*

	Type A	Type B	Type C
Occurrence	At onset	Several days later, average of 5 days	After 6th day
Joints involved	Symmetric polyarthritis, almost all joints and extremities	One joint, usually knee	One or several
Pathologic data	Hemorrhage, periarticular or intra articular	Purulent arthritis	Serous arthritis
Bacteriologic data	Exudate not examined	Meningococci in $\frac{1}{2}$	Negative
Pain	Severe	Moderate	Moderate
Redness	Marked	Slight or absent	Moderate
Swelling	Slight or absent	Marked	Moderate
Tenderness	Marked	Slight	Moderate
Spasm	Marked	Slight	Moderate
Type of infection	Fulminating and severe	Mild or moderate	No relation
Rash on skin	Hemorrhagic	Inconstant	Urticarial, erythema
Duration	Short	Long	Short
Complications	Panophthalmia, epididymitis, etc	Infrequent	Serum sickness
Prognosis	Poor	Good	Good
Treatment	General serotherapy	Serum, general and local	Rest

gonorrheal arthritis or some other disorder. Several such cases will be presented.

(b) It may occur during the acute meningitis.

(c) Finally, it may occur after the meningeal symptoms have subsided, usually from the fourth to the seventh day of the infection but at times anywhere up to the thirty-fifth day.

II Meningococcic infection of the joints may occur, with sepsis, apart from the meningitis. None of the present cases were of this type, although a few appeared so until the late appearance of meningitis.

III It may occur as an isolated localized infection, with no other foci in the body. None of the present cases were of this type. These constitute the rarest ones, examples of which are reported by Weill, Dufourt and Bocca¹⁶ (even autopsy showed no meningitis or sepsis), Kobayashi¹⁸ and Campbell and Greenfield.¹⁹ Of course, mild meningitis or sepsis might easily have been missed.

PATHIOLOGY

The inflammation is mainly periarticular in the ordinary cases, as studied post mortem by Still, Osler and the French workers (quoted by Herrick and Parkhurst¹⁵) In the early, arthralgic, rheumatic or polyarthritic type of case (group A) the lesions are hemorrhagic, corresponding with the purpuric spots in the skin and causing articular irritation from their location in the synovial structures resembling Schonlein's purpura These nearly always subside, but at times the organisms gain a foothold and produce a more typical true arthritis and/or periarthritis, usually in one but occasionally in several joints (group B)

The type of inflammation varies, exactly as in gonorrheal arthritis, from mild serous to seropurulent, subacute plastic, frank purulent and acute destructive forms The outcome is by no means uniformly favorable, depending on the severity of the local lesions and the efficacy of the specific treatment Destruction and ankylosis do occur

CLINICAL CHARACTERISTICS

From table 1, as well as the literature, it is seen that the age, sex, severity of the general infection, duration of the infection and type of treatment (excluding the more recent specific antitoxic antiserum and sulfanilamide, which cannot as yet be accurately evaluated) have no influence on the severity, frequency, duration or joints involved in the arthritic lesions In 2 cases the articular manifestations preceded the meningitis, and in several others the meningeal signs were of such low grade, compared with the accompanying arthritic symptoms, that the diagnosis was confused These cases will be detailed later In the remaining cases the onset of articular manifestations ranged from the second or third day after full-blown meningitis to as late as four weeks In case 3 obvious articular involvement was present only after two and one-half months, but the patient was in such prolonged stupor and the lesions were so deeply placed that it is likely that this involvement had been overlooked until then Over half the patients showed articular involvement between the fifth and the twelfth day after onset of the general infection Serum sickness occurred in 11 cases, with several others questionable, swelling of the joints being the only symptom

The joints involved in this series, in the order of their frequency, were

No of Cases		No of Cases	
Knee	9	Ankle	4
Hand	7	Hip	3
Elbow	6	Tarsus	1
Wrist	5	All joints	3

Of the joints which became badly destroyed, the elbow was involved in 2 cases, the hip in 2, the wrist in 1 and the knee in 1 Involvement

of the knees and hands tended to be more arthritic than arthralgic, with effusion and much periarticular infiltration. According to Rolleston, in young children the small joints of the hands and feet are prone to be attacked. This held true with respect to the infant in the present series. In the ordinary type of infection (group B) involvement of the knees predominates by far.

GROUP A (TABLE 2) CASES IN WHICH THE MORTALITY IS HIGH BUT THERE IS SCANT ARTICULAR INVOLVEMENT

These cases are of the polyarthritic, arthralgic, "rheumatic" type, the articular symptoms occurring in the first few days of generalized infection, not infrequently before the full-blown meningeal picture is obvious. This type of condition usually accompanies the meningococcemic form of the disease, with a severe rash and stormy course, although the articular manifestations are often transient. This corresponds with small, petechial hemorrhages adjacent to and within the joints. There may be slight effusion, but considerable pain and tenderness are characteristic, and other metastatic complications, such as endocarditis, panophthalmia, deafness and endocarditis, are common. Occasionally, after a few days, instead of subsiding, the symptoms merge with those noted in the cases in group B and even group C.

Herrick and Parkhurst reported 12 such cases, with death occurring in one third of them. The wrists and knees were mainly involved, with the ankles and elbows next in order. In 2 cases meningitis was not present. Cecil and Soper²³ reported 4 cases of meningococcal sepsis with arthritis but without meningitis. Except for that, they resembled the present cases. In preparing this report, a separate group of cases of chronic meningococcemia and meningitis were investigated both at Bellevue Hospital and at Mount Sinai Hospital, but in none was arthritis found. In most of them arthralgias were mentioned, but there was not enough inflammation to warrant a diagnosis of arthritis. Nevertheless, in any case of prolonged fever with obscure polyarthritis, meningococcemic infection without meningitis must be suspected and proper bacteriologic studies undertaken.

It will be obvious how in some of these cases the condition resembles other, more common types of arthritis, making the differential diagnosis, especially before meningeal signs appear, difficult. The great resemblance to gonorrheal arthritis and rheumatic fever must, above all, be emphasized.

CASE 16—A 42 year old man entered the hospital with a fulminating general infection. Cardiac valvular disease was discovered at once, and the problem of rheumatic activation was presented. Diffuse polyarthritis began on the second

23 Cecil, R. L., and Soper, W. B. Meningococcus Endocarditis, with Septicemia. Its Bearing on the Mode of Infection in Epidemic Cerebrospinal Meningitis, *Arch. Int. Med.* 8:1 (July) 1911.

day and spread to involve all the joints, but chiefly the wrists and knees. In addition, two gonorrheal complement fixation tests of the blood showed a 3 plus reaction, and for a time the diagnosis of gonorrheal arthritis was favored. It was only with the appearance of frank meningitis and culture of meningococci in the spinal fluid that the true nature of the inflammation was suspected, about a week after entry. The meningitis responded at once to large doses of serum intrathecally and intravenously, but the arthritis ran a prolonged course, lasting three months, with final complete recovery. On one occasion specific antiserum was injected into the more severely involved knee.

Comment—This case illustrates some of the difficulties of making a diagnosis in the absence of meningitis. The presence of gonorrheal arthritis was strongly suspected, as well as reactivation of old rheumatic fever, until similar organisms from the spinal fluid and from the knee were shown to be meningococci.

CASE 17—A 3 year old boy presented signs of severe meningeal and meningococcemic involvement, with marked coma, cutaneous signs and diffuse articular inflammation, from the third day of the illness. Culture of the spinal fluid showed meningococci, but, despite the administration of large doses of serum intraspinally and intravenously, the boy died on the sixth day.

CASE 22 (Dr J. Wishner has given me permission to report this case)—A middle-aged woman entered the hospital with a history of chills, fever and arthritis of both wrists and ankles of four days' duration. The temperature was high, and there was a rash. The knees were involved soon after entry. Blood culture, as well as the general laboratory study showed no abnormality. Both knees were aspirated, and culture of the fluid and smears did not show meningococci. Plaster splints were applied to the knees and ankles in the second week. It was only in the third week that meningitis appeared and the spinal fluid was found to contain meningococci. Serum was given intraspinally, and both the meningitis and the arthritis cleared up one month after entry. The patient made a complete recovery.

Comment—These cases also illustrate the diagnostic errors that may be made in cases of meningococcic "rheumatism" without meningitis. The articular involvement was followed by meningitis in about two and a half weeks, and it was only then that the correct diagnosis was made. This premeningeal picture corresponds exactly with that described by Sainton and Herrick.

GROUP B CASES OF THE COMMON TYPE, IN WHICH GROSS INFLAMMATION OF THE JOINTS IS PRESENT

The characteristics in this group are given in table 2. The symptoms occur mainly after the fifth day. When they coincide with the manifestations of serum sickness and are mild, they may be mistaken for those observed in the cases in group C. These are the cases in which the involvement is characteristically monoarthritic, if it is multiple, one joint is more involved than the others. Effusion is the outstanding feature, with much swelling, but there is relatively little pain, tenderness or limitation of motion. This is mentioned as characteristic of meningococcic involvement of the joints by nearly all the authors who have been

consulted While true frequently, it is by no means invariably true, depending entirely on the severity of the infection In several of the cases in this series the pain required morphine and splinting, and flexion contracture occurred In the cases of destructive involvement, swelling, heat, pain and local inflammation were marked, and limitation of motion was extreme Much is made in the literature of a typical articular fluid However, little difference is seen between this exudate and the inflammatory exudates obtained in cases of acute infectious arthritis of other types The fluid varies from mucinous, serous, to seropurulent and may even, uncommonly, contain thick pus It is often hemorrhagic and brown, because of the presence of old blood Meningococci are cultured in one-third to one-half the cases and on smear may be both extracellular and intracellular The fluid contains a preponderance of polymorphonuclears and an increased amount of protein

Herrick and Parkhurst reported 16 cases of this type, and Sainton in his various reports mentioned a total of 17 cases In both series and in the present one the knee was by far the most often involved The mortality in these cases was less than that in the cases in group A and less than the general average mortality in epidemic meningitis, although the articular involvement was more severe At least 14 of the present cases fall in this group Fluid was aspirated in 6 of these cases, and meningococci were grown in 3 cases (fluid from the knee in 2 cases and from the wrist in 1 case), in the 3 other cases the fluid was obtained from the knee

CASE 1—A 49 year old man entered the hospital with a three day history of fever, cramps and other symptoms Several purpuric spots and early signs of meningitis were present On lumbar puncture cloudy fluid was obtained which showed gram-negative diplococci on smear, though culture was sterile Other laboratory studies showed a high leukocyte count, with an increased number of polymorphonuclears The patient was given antiserum intravenously and intrathecally and recovered fairly well in about a week Four days after entry, inflammation of the dorsum of the left foot appeared, with redness, swelling, pain and tenderness The symptoms did not fluctuate, and after ten days a roentgenogram revealed evidence of atrophy and arthritis about the tarsal and metatarsal joints The lesion gradually subsided with no local therapy except short wave diathermy The patient also had a mild serum reaction

CASE 4 (reported by Jaffe¹⁷)—A 66 year old Italian had had arthritis with fever thirty years before He was known to have had syphilis two years before and was admitted because of a "postarsphenamine reaction," with jaundice, chills, fever of three weeks' duration, and pain, swelling and inflammation of the right wrist and ankle for ten days Physical examination showed much periartthritis and arthritis, with swelling and infiltration of the right wrist and ankle The Wassermann and Kahn tests of the blood gave a 4 plus reaction At first the patient was believed to have arsphenamine hepatitis and gonorrheal arthritis, recent exposure having been admitted Aspiration of fluid from the right wrist revealed intracellular gram-negative diplococci, apparently confirming the diagnosis However, a day or two later, signs of meningeal involvement appeared, confirmed by lumbar puncture, and meningococci were cultured from the spinal fluid and the

fluid from the wrist (immunologically verified) The patient improved with anti-serum treatment, after ten days the joints were normal, and the meningitis subsided Two weeks later a recrudescence of the arthritis in the wrist occurred with fever but no meningitis, and the patient died in stupor, with jaundice and confluent bronchopneumonia, confirmed by autopsy

Comment—Again it is illustrated how readily confusion with gonorrheal or other types of infectious arthritis is possible In this case, only identification of the organisms by agglutination and agglutination absorption tests made the diagnosis definite

CASE 15—A 20 year old man, a deaf-mute, was transferred from another hospital to Bellevue Hospital after cerebrospinal meningitis, which had been successfully treated by lumbar puncture and with serum, although culture and smears had not shown meningococci Serum sickness developed on the sixth day and inflammation of the right knee three days later This was not serum arthritis but acute arthritis, the knee being held in semiflexion, with only 5 to 10 degrees of motion Fluid, periarticular infiltration and local heat were marked The spinal fluid at this time was normal Fluid from the knee was sterile but was typical articular exudate The fever was low grade for two weeks, the curve then becoming flat After one puncture of the knee the fluid disappeared Traction was applied after a week or two, and gradually the deformity and arthritis subsided, aided by mild physical therapy with complete recovery of all motion

CASE 5—A 44 year old woman was acutely ill with typical severe meningococcic meningitis She presented a picture of peritoneal irritation and generalized petechial rash The spinal fluid contained meningococci, but blood culture was sterile The fever subsided at once with specific therapy (lumbar punctures and serum), and the spinal fluid became normal, with subsidence of the meningitis in five days Ten days after entry, severe arthritis of the right knee developed, the diagnosis being verified by aspiration and culture of meningococci from the fluid from the knee The temperature rose to 102 F With aspiration and splinting, the tendency to flexion contracture and mucopurulent effusion was gradually overcome At the time of the patient's discharge from the hospital, the knee was fairly stiff A follow-up report after one year revealed limitation of only 10 degrees of flexion

GROUP C CASES OF MILD INVOLVEMENT OF THE JOINTS RESEMBLING THAT IN SERUM SICKNESS

This group includes those cases in which the condition was confused with or actually due to serum sickness Herrick and Paikhurst presented 12 cases, the manifestations being similar whether serum was given intramuscularly, intravenously or intrathecally In the present series this difficulty with regard to the differential diagnosis occurred about half a dozen times (cases 8, 9, 11, 13 and 14) It is my opinion that in most of these cases the involvement of the joints was meningococcic and not due to serum sickness, however, I have no definite proof of this One patient (case 6) apparently had both serum sickness and meningococcic involvement of the joints

This difficulty in making a differential diagnosis is inherent in the time of occurrence of the serum sickness and in the nature of the articular involvement, duration of symptoms and general characteristics,

when compared with the characteristics of the less severe forms of the group B type of meningococcic arthritis Table 2 gives the main features of this condition, but none of the points mentioned serve to establish the differential diagnosis A serum reaction has been common in meningitis, as until recently in all cases during an epidemic treatment with antiserum has been given as soon as the diagnosis has been made, usually crude serum has been used Rolleston¹³ said the incidence was 67 to 81 per cent in 1919 and before Bolduan²² said it was 52 per cent in the Bellevue Hospital series of children

Rolleston¹³ stated that the urticarial rash is the most common finding but that serum arthritis does occur, involving one or more joints before, during or, usually, three days after the rash, and consists of pain and stiffness rather than swelling Coca, quoted by Duke,²⁴ said that the incidence of articular pain and tenderness in a large series of cases of serum sickness was from 1 to 19 per cent, with involvement of the fingers and hands mainly Mackenzie²⁵ stated that serum disease without cutaneous manifestations is rare and that the condition is characterized by pain and stiffness of the joints, with little to be felt or seen, although in rare cases local swelling, heat and other symptoms, simulating those of rheumatic fever may be present Schick,²⁶ who, with von Pirquet, published the most widely quoted work on serum disease and described a large number of cases of serum sickness, stated that articular pains seldom occur but can be intense and annoying, involving large or small joints, often only one joint, the condition being marked by transience and absence of objective symptoms

It is obvious, then, that if meningococcic arthritis occurs in the second week of the disease and serum sickness seven to ten days after the first dose of serum is given, the two conditions will often coincide, and, if the clinical condition is not severe, great difficulty will be encountered in making a differential diagnosis Much depends on the occurrence and time relation of an accompanying rash, although both conditions can exist in one patient Fortunately, the distinction is not often of practical importance, as, if the articular involvement is mild enough to be suspected as being due to serum sickness, the prognosis of the arthritis is excellent regardless of therapy In the following case both types of involvement were probably present

CASE 6—An 11 year old boy entered with the clinical picture of cerebrospinal meningitis, with numerous petechiae The appearance of the spinal fluid was typical, and he was given intrathecal injections of serum daily Smears and

24 Duke, W W Allergy, Asthma, Hay Fever, Urticaria and Allied Manifestations of Reaction, ed 2, St Louis, C V Mosby Company, 1925

25 Mackenzie, G M Serum Disease, in Cecil, R L A Textbook of Medicine, Philadelphia, W B Saunders Company, 1927, p 468

26 Schick, B Serum Disease, in Brennemann, J Practice of Pediatrics, Hagerstown, Md, W F Prior Company, Inc, 1937, vol 2

culture gave positive evidence at first. On the fifth day, generalized articular pains appeared in the right wrist, left hand, both knees and the right shoulder, along with lymphadenopathy and swelling of the hands, all suggestive of an extensive serum reaction. The right knee then swelled up. He was treated for serum sickness, with gradual subsidence of all symptoms except those in the right knee. Urticaria appeared at the height of the articular involvement, and elevation of the temperature and inflammation of the knee persisted, along with deafness. Fluid was aspirated from the knee twice, and then transient pain in the left hip and involvement of the right ankle and foot appeared. After this, with further specific therapy, gradual improvement of all the joints occurred, with complete recovery and discharge in five weeks.

GROUP D CASES OF SO-CALLED POSTMENINGITIC SPONDYLITIS

This loose entity is described by Epstein^{20a, b} in two reports, in which he presented 2 cases in which there was productive spondylitis, between the bodies of the third and fourth lumbar vertebrae, with narrowing of the intervertebral disks and some destruction of the third lumbar vertebra. One patient also had a residual drop foot. He attributed these 2 cases to direct meningococcic invasion of the spinal bodies, on a metastatic basis. One patient was followed over a year before narrowing of the disk became obvious.

Billington,^{20c} following Epstein's lead, reported a group of cases of "spondylitis after meningitis," including 35 cases of pain in the back after epidemic meningitis. He divided them into cases in which osteoarthritis was noted roentgenographically (in 8 cases there was narrowing of the disk between the third and fourth lumbar vertebrae, and in 12 there wasipping of the vertebral margins), cases in which no changes were noted roentgenographically but in which positive physical signs were present, and, the largest number, cases in which symptoms were present in the back but no objective signs were noted. In only 1 of these cases was arthritis (in the wrist alone) present during the meningitis.

In view of the present knowledge of the physiology and pathology of the intervertebral disks, it seems that the aforementioned findings can be explained better than by being attributed to meningococcic invasion. It is much more likely that the frequent lumbar punctures required in treating the disease according to standard methods caused injury to the posterior limiting portion of the annulus fibrosus of the intervertebral disk, thus allowing prolapse of the nucleus pulposus and giving rise to both the signs and the symptoms mentioned. Similar cases have been reported after an operation in which spinal anesthesia has been used, and the greater relative frequency after meningitis may simply be due to the greater number of lumbar punctures in each case.

PROGNOSIS AND TREATMENT

All the authors who have presented groups of cases of meningococcic arthritis, including Netter and Duand, Santon, Rolleston, and Herrick

and Parkhuist, have emphasized the innocuousness of this condition and its fine prognostic import, both as to the outcome of the articular infection and the general infection. They and all the authors of textbooks consulted have stated that resolution is the only result to be expected, other sequelae being extremely rare. Before presenting 3 cases from this series in which the joints were permanently destroyed, a brief summary of reports of other cases gathered from the literature will be given.

Herrick¹⁵ described 1 case in which the wrist was involved, with necrosis of the base of the radius, and another in which orthopedic measures had to be used to relieve a marked flexion contracture of the knee. Netter and Durand²⁷ said all their patients recovered uneventfully, though 1 had an arthrotomy of the knee. Santon and Bosquet²⁸ reported on a child with suppuration of the shoulder and knee, with ultimate destruction and ankylosis of the shoulder, despite surgical drainage. Netter and Josias (quoted by Roger²⁹) reported ankylosis of the shoulder in an infant after arthrotomy. Roger²⁹ reported a case of subacute suppurative meningococcic arthritis of the hip and knee in a young soldier, which went on to fibrous ankylosis of both joints, noted three years later. This occurred despite the most careful after-treatment, including attempts at early mobilization, traction, plaster immobilization, manipulation under anesthesia, early specific therapy and aspiration, the behavior being exactly like that when the joints are severely involved in gonorrhea. Weill, Dufourt and Bocca¹⁶ reported a fatal case in an infant of 17 days who had suppuration of the left knee and sternoclavicular joint, resulting in a large cervical abscess from which meningococci were cultured.

CASE 3—A 17 year old girl entered with a four day history of meningeal symptoms, found to be due to typical meningococcic meningitis, with accompanying arthritis of the right wrist and left finger joints before entry. Lumbar puncture confirmed the diagnosis, and the organisms were grown from the spinal fluid. Neurologically the course was complicated by development of an encephalitic picture involving the midbrain, cerebellum and corpus striatum, with complete disorientation. While the arthritis was somewhat overlooked in view of the neurologic aspects of the case, after two months severe disease was noted in the right hip and left elbow. Both of these joints were permanently damaged. She was transferred to another institution, where the hip was found to be fairly stiff, and the elbow became ankylosed after arthrotomy.

CASE 12—A 19 year old girl was admitted to the gynecologic service because of severe abdominal pain with chills. On the second day meningitis appeared, with typical changes in the spinal fluid, and the patient was transferred to the medical service. She was treated at once with lumbar puncture and antiserum

27 Netter, A., and Durand, H. *Bull Acad de med, Paris* **73** 441 (April 13) 1915

28 Santon, P., and Bosquet, J. *Bull et mem Soc méd d hôp de Paris* **40** 344 (March 17) 1916

29 Roger, H. *Marseille-med* **55** 505 1918

intrathecally. The arthritis began on the fifth day, with severe pain and swelling in the wrist, which was huge. She was treated after a time by plaster immobilization, but as the meningitis subsided, severe arthritis appeared in both elbows and the other wrist. Fever therapy, transfusions and other treatment were given, but the course was stormy. Little fluid appeared within the joints, the inflammation being dry and periarticular. After one hundred and three days the patient left the hospital with complete ankylosis of the right elbow and left wrist and partial ankylosis of the left elbow, all in satisfactory position (as placed in the original plaster splinting with the patient under anesthesia, when the joints were destroyed).

Comment—In case 12 there was the most severe meningococcic infection of the joints which I have come across, and I was thereby stimulated to collect the material for this paper. The only type of therapy the patient did not have which was available at that time was intra-articular injection of serum.

CASE 23 (Dr R. K. Lippmann gave me permission to report this case).—A 48 year old woman, a graduate nurse, entered with typical signs of acute meningitis of one day's duration. Numerous petechiae were present. Lumbar puncture confirmed this diagnosis by smear and culture, and specific therapy was begun with antiserum intrathecally and intravenously. On the fourth day after entry, when the signs of meningeal involvement were subsiding, arthritis of the right knee appeared. Serum sickness appeared on the seventh day. The knee was aspirated, and culture and smear of the fluid revealed no meningococci. Fever therapy was instituted, plus local diathermy for two treatments, as for treatment of a gonorrheal infection. Involvement of the hip appeared in the sixth week, and traction was applied to prevent flexion of the knee. Low grade involvement of the knee and hip with fever lasted until a cast was applied for relief of pain. On re-entry, roentgenograms showed destructive changes in the femur and tibia at the knee and marked destruction of the head and neck of the femur. A second plaster spica was applied to the hip and knee for two months, after which the pain was greatly diminished. Subsequently, firm fibrous ankylosis of both joints resulted. This became bony fusion after one year.

Comment—In addition to these cases, the severity of meningococcic invasion of joints is attested by the fact that in 6 cases aspiration was necessary, in 4 cases splinting with circular or molded plaster splints was resorted to and in 2 cases traction was employed to correct flexion deformity of the knee. In only 1 case was antiserum injected intra-articularly, as recommended by Netter and DuRand and by Santon.

Death occurred in 3 cases, probably a lower mortality than for the general series of cases of meningeal involvement. In none did the arthritis have any relation to an ultimate fatal outcome. Indeed, this confirms the benign prognosis given in the literature as to the outcome of the general infection in patients who show the arthritic complication. Other associated complications were relatively few, there being 2 cases of nodocyclitis, 1 of encephalitis, 1 of deafness and 2 of acute otitis media.

A significant finding is that all the more severe articular manifestations occurred in persons more than 12 years of age, including the cases in which ankylosis resulted and those in which orthopedic treatment was required. In children, then, the outcome of meningococcic arthritis is truly benign, but in adults it is by no means so.

It is also of great therapeutic interest that in recent series of cases of meningitis in which antitoxic antiserum (Hoyne) was given, there has been a lower incidence of complications in general and of arthritis in particular, as well as a lower mortality rate than in controlled series in which ordinary antiserum was employed. Thus Tucker³⁰ reported an epidemic in which ordinary antiserum therapy in 16 cases resulted in 10 deaths, while antitoxin in the next 53 cases caused only 15 deaths. He used it intravenously and reported only 1 case of meningococcic arthritis in the entire series of 69 cases. Similarly, Petty³¹ reported an epidemic of 95 cases, with a 6.5 per cent mortality and a low rate for complications, with no meningococcic arthritis. It is possible, then, that the newer types of treatment, including the use of antitoxic antiserum and possibly sulfanilamide, may change this picture and actually eliminate meningococcic arthritis, at any rate in its ankylosing forms.

SUMMARY AND CONCLUSIONS

A complete review of the literature on meningococcic arthritis is presented, with an analysis of 23 cases from a large number of cases of meningococcic infection.

Classification is made, according to the criteria of Herrick and Parkhurst, into three main groups: (1) the early, often premeningitic, polyarthritic or arthralgic type of involvement, (2) the ordinary post-meningitic monoarthritic type, and (3) the type resembling serum sickness. It is further pointed out that intermediary and atypical types abound. Illustrative cases are presented.

The resemblance of the pathologic and clinical picture in many cases to that of gonorrheal and other arthritic disorders is emphasized.

Whereas in the literature the prognosis is said to be uniformly favorable with few exceptions (which are given), 3 of 23 cases are presented in which articular destruction and ankylosis eventually resulted, as well as others in which various types of orthopedic treatment were required.

The prognosis of the articular complication is much better for children than for adults.

The possible effect of recent refinements in the therapy of meningococcic infections on prognosis and prophylaxis is pointed out, especially as regards the efficacy of meningococcic antitoxin (Hoyne).

30 Tucker, W. H. *Illinois M. J.* **71** 328 (April) 1937.

31 Petty, C. R. *Kentucky M. J.* **35** 180 (April) 1937.

CIRCULATION DURING PREGNANCY

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The studies reported here deal with some of the alterations which take place in the maternal circulation during pregnancy. The first part of the report deals with observations bearing on the work of the heart during pregnancy and is particularly concerned with the cardiac output, the second part describes certain physical signs reflecting the state of the circulation, the third part reports a study of the venous pressure in the pregnant woman, the fourth part deals with certain related observations on animals and the final section discusses some of the mechanisms which underlie the phenomena observed. A discussion of the more general aspects of the problem has been presented elsewhere¹

I THE OUTPUT OF THE HEART AND SOME RELATED OBSERVATIONS

Although the earlier literature concerned with the circulation during pregnancy contains many statements to the effect that the amount of blood pumped by the heart must be increased, the first measurement was reported in 1915 by Lindhard². This investigator, using the nitrous oxide method of Krogh and Lindhard,³ determined the cardiac output

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1 Burwell, C S. The Placenta as a Modified Arteriovenous Fistula Considered in Relation to the Circulatory Adjustments to Pregnancy, *Am J M Sc* **195** 1, 1938

2 Lindhard, J. Ueber das Minutenvolum des Herzens bei Ruhe und bei Muskelarbeit, *Arch f d ges Physiol* **161** 233, 1915

3 Krogh, A, and Lindhard, J. Measurements of the Blood Flow Through the Lungs of Man, *Skandinav Arch f Physiol* **27** 100, 1912

of a normal woman before, during and after pregnancy. An increase in the output of about 50 per cent was observed during pregnancy, with a return to the previous level after delivery. The significance of these observations was somewhat obscured by the presence of moderately severe anemia during the period when the output was increased.

Weiss⁴ reported in 1924 a series of observations concerning cardiac work. He measured the blood pressure as well as the cardiac output of 8 women during the last weeks of pregnancy. These determinations were not repeated after delivery, the results were compared with "average" figures for nonpregnant women. Weiss concluded that during this stage of pregnancy there are a normal blood pressure, an increase in the cardiac output of from 45 to 85 per cent and a diminished arteriovenous difference. He used the nitrous oxide method in determining the output.

Using the same method, Gammeltoft⁵ determined the cardiac output of several normal women during pregnancy and the puerperium. One of these patients was studied on twelve occasions between the eighth and the thirty-ninth week of pregnancy. A gradual rise in output until the thirty-third week was observed. The values determined in the thirty-fifth, thirty-seventh and thirty-ninth weeks were somewhat lower, and during this period the arteriovenous difference, which had been at its minimum (39.8 to 42.3 cc per liter) from the twenty-fourth to the thirty-third week, rose to nearly normal levels (46.7 to 57 cc per liter). The striking changes in these late weeks Gammeltoft attributed to the fact that the patient had given up work and was resting at home.

In 1928 Marshall and Grollman⁶ introduced the acetylene method for the determination of the cardiac output in man. The relative simplicity of the cooperation required of the patient and the relative reliability of the method (at least as applied to resting patients) led to its application in many conditions, including pregnancy. In 1932 Stander and Cadden⁷ reported determinations of the cardiac output at various stages of pregnancy and the puerperium in 13 normal women and 4 women with heart disease or nephritis. For 4 of the normal women and 1 of the patients with nephritis, observations were made both before and after delivery. On the basis of their observations these authors concluded that "from the fourth month of pregnancy to full term there

4 Weiss, R. Ueber die Mehrleistung des Herzens während der Schwangerschaft, *Klin Wchnschr* **3** 106, 1924.

5 Gammeltoft, S. A. Recherches sur le débit cardiaque par minute pendant la grossesse, *Compt rend Soc de biol* **94** 1099, 1926.

6 Marshall, E. K., Jr., and Grollman, A. A Method for the Determination of the Circulatory Minute Volume in Man, *Am J Physiol* **86** 117, 1928.

7 Stander, H. J., and Cadden, J. F. The Cardiac Output in Pregnant Women, *Am J Obst & Gynec* **24** 13, 1932.

is a steady increase in cardiac output amounting to over 50 per cent of the normal value”

Schmidt,⁸ in 1932, made significant additions to the knowledge of the circulation in pregnancy by applying the Grollman procedure to the elucidation of certain specific problems. He determined the cardiac output of 5 women before and after therapeutic abortion. Although in 4 of the cases the determinations were made only during the early months of pregnancy (up to the third or fourth), in each case the cardiac output was higher during pregnancy than after abortion (33 to 67 per cent). The termination of pregnancy in these cases was advisable because of noncardiac disease, 3 of the patients having tuberculosis. Five women with valvular disease but without cardiac failure were studied in the same way. They were observed in the second to the fourth month of pregnancy and after therapeutic abortion. There was more variation in successive determinations for the same individuals in this group of patients than there was for a normal group. Four of the 5 showed a cardiac output during pregnancy which was 21 to 72 per cent greater than that observed after abortion. The exception (the cardiac output averaged 3.6 liters before and 3.5 liters after abortion) was a woman in the third month of pregnancy who had aortic and mitral disease. Schmidt also made some observations on the changes in cardiac output produced by a given amount of exercise during early pregnancy and after delivery. Four women were studied during exercise, 2 of them having valvular disease but without failure. All 4 showed during pregnancy a greater increase in cardiac output after exercise than they showed when similar exercise was undertaken after the uterus was emptied. The method was modified for use with exercising patients, but there is nevertheless a larger possibility of error (due to recirculation) in the application of the acetylene method to the determination of cardiac output during exercise than in its use during rest.⁹

Other contributions have been made by Liljestrand and Stenstrom¹⁰ and by Haupt.¹¹

To these observations of the cardiac output during pregnancy in women may be added the observations of Stander, Duncan and Sisson.¹²

8 Schmidt, R. H. Ueber die Herzarbeit in der Frühschwangerschaft in der Ruhe und nach Arbeitsversuchen, *Monatschr. f. Geburtsh. u. Gynäk.* **90**:83, 1932.

9 Grollman, A. *The Cardiac Output of Man in Health and Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

10 Liljestrand, G., and Stenstrom, N. Clinical Studies on the Work of the Heart During Rest. III. Blood Flow in Cases of Increased Arterial Blood Pressure, with Observations on the Influence of Pregnancy on the Blood Flow, *Acta med. Scandinav.* **63**:142, 1925-1926.

11 Haupt, W. Das Minutenvolumen des Herzens bei Wöchnerinnen, *Arch. f. Gynäk.* **132**:33, 1927.

12 Stander, H. J., Duncan, E. E., and Sisson, W. E. Heart Output During Pregnancy, *Am. J. Obst. & Gynec.* **11**:44, 1926.

on dogs. These observers applied the direct Fick method described by Marshall¹³ to the determination of the cardiac output of 2 bitches before, during and after pregnancy. An increase in output was observed that was comparable to that reported for women.

METHODS

Four intelligent young women in the early months of pregnancy were selected, their cooperation was enlisted and they were trained as subjects. Observations were begun in the third or fourth month of pregnancy and were repeated at intervals of two to six weeks throughout pregnancy and during the puerperium. The cardiac output was determined by the acetylene method of Marshall and Grollman⁶. The two sample method was used, since at the time the studies were made the importance of the three sample method had not yet been emphasized by Grollman, Friedman, Clark and Harrison¹⁴. The usual standard "basal" conditions in regard to rest and food were observed, i.e., the subject came to the laboratory at 8 a.m., having taken no food during the previous twelve hours, and then rested in a semi-reclining position in a wheel chair for an hour previous to the test. The oxygen consumption was measured by collecting the expired air in a large spirometer of the Tissot type and analyzing it (in duplicate samples) in a Haldane apparatus. During the "basal" period the blood pressure and pulse rate were also recorded. At the conclusion of the observations concerned with oxygen consumption and cardiac output, the vital capacity was measured.

At frequent intervals throughout pregnancy certain additional studies were made. These included observations of physical signs, roentgenograms and electrocardiograms and the determination of the erythrocyte and hemoglobin contents of the blood.

The histories are summarized briefly herewith.

REPORT OF CASES

CASE 1—The patient, aged 27, was observed during her first pregnancy. There was no history suggestive of heart disease or of attacks of rheumatic fever. She was 147 cm. tall and weighed 56 Kg. On the initial examination the findings concerning her heart were as follows. There was a forceful impulse. The cardiac dulness extended 3.5 cm. to the right and 8 cm. to the left in the fifth space. The sounds were loud. There was a faint blowing systolic murmur at the apex but no diastolic murmur. The blood pressure was 120 systolic and 86 diastolic. During pregnancy she continued to exercise. A month before delivery the apex was in the fourth space and well outside the midclavicular line. The pulmonic second sound and the apical first sound appeared louder than previously. The systolic murmur was a little louder. Delivery was uneventful, and examination afterward revealed an apparently normal heart.

13 Marshall, E. K., Jr. Studies on the Cardiac Output of the Dog. I. The Cardiac Output of the Normal Unanesthetized Dog, *Am J Physiol* **77** 459, 1926.

14 Grollman, A., Friedman, B., Clark, G., and Harrison, T. R. Studies in Congestive Heart Failure. XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J Clin Investigation* **12** 751, 1933.

CASE 2—The patient, aged 25, was observed during her first pregnancy. Her health had been good, but ten years before she was seen she had been in bed for a week with painful, swollen and tender joints. There was a mild recurrence a year later. Ten months before she was seen she was told by a physician that she had heart disease. Physical examination at the eleventh week of pregnancy showed that she was of small stature and slender build. Her height was 162 cm and her weight 47.2 Kg. Examination of the heart showed a localized apex beat in the fifth interspace. There was no thrill. The sounds were of good quality, and both the mitral first and the pulmonic second sound were loud. A loud blowing systolic murmur was audible at the apex. No diastolic murmur was heard. After exercise the acceleration was not excessive, and slowing was prompt. No evidence of peripheral congestion was ever present. A teleroentgenogram revealed a somewhat globular heart, with a total diameter of 12 cm, and a thoracic diameter of 24 cm. No new signs developed during the remaining months of pregnancy except slight displacement of the heart. After delivery the cardiac signs were similar to those observed on the first examination. At no time was a diastolic murmur heard or were any symptoms or signs of cardiac failure present. The history of rheumatism, the globular heart, the systolic murmur which persisted after delivery and the possible slight enlargement of the heart were interpreted as indicating mitral disease with regurgitation.

CASE 3—The patient, aged 24, was observed during her first pregnancy. She had scarlet fever at 6 and frequent attacks of tonsillitis until 11 years of age. She was a small, alert woman. She was 158 cm tall and weighed 51.5 Kg. The heart was not enlarged, and the sounds were of good quality. A systolic murmur was heard at both apex and base, being louder at the pulmonic area than elsewhere. During the course of the pregnancy the apex beat became more vigorous and thrusting, and the sounds became louder. No diastolic murmur was ever heard. After delivery the apex beat was less forceful, the sounds were less loud and the murmurs were diminished.

CASE 4—The patient, aged 24, was observed during her second pregnancy. She had had diphtheria at 12 years of age, but her health had been good except for recurrent attacks of migraine since the age of 14. She was a slender, rather tense woman. She was 172 cm tall and weighed 60.8 Kg. Examination of the heart showed a vigorous impulse, with a slight systolic thrill at the apex. The heart was not enlarged. There was a moderately loud, blowing systolic murmur, heard best at the apex and loudest late in systole. It was also heard at the base. The cardiac findings did not change materially except that evidence of overactivity became less marked just before delivery. After delivery the systolic murmur was not heard.

In these notes concerning individual patients it will be observed that 1 of the 4 exhibited signs interpreted as pointing to the presence of rheumatic mitral disease with regurgitation, the others showed no signs that were accepted as evidence of the existence of heart disease.

RESULTS

The results of observations in these 4 cases are summarized in tables 1 to 4 and in the case records. Certain groups of findings may be selected for comment.

The Heart Rate—It has long been known that pregnancy is associated with elevation of the pulse rate and that delivery is followed by slowing. In our 4 patients the heart rate was observed under standard conditions. Each figure in tables 1 to 4 represents an average of several thirty-second counts. In table 5 is shown for each patient the average

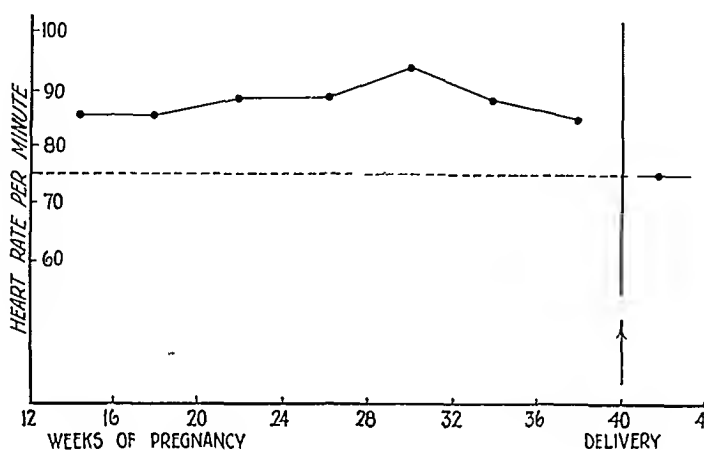


Fig 1—The pulse rate from the fourth to the tenth month of pregnancy and in the puerperium

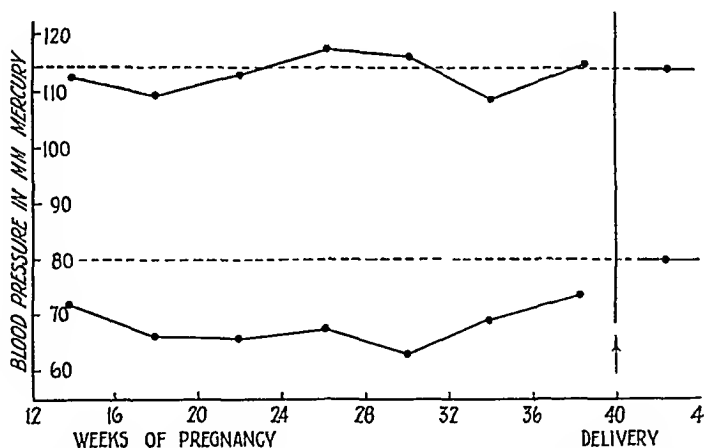


Fig 2—The blood pressures in the fourth to the tenth month of pregnancy and in the puerperium

of all such counts during pregnancy compared with the average of counts made post partum. In 3 of the 4 patients the basal pulse rate was from 12 to 28 beats per minute higher during pregnancy than after its termination. In the fourth patient the situation was reversed. The heart rate of 93 per minute recorded after delivery may have been influenced by the fact that she was observed only on the ninth and tenth days post

TABLE 1—Data for E E (case 1)

Week of Preg-nancy	Oxygen Con-sump-tion, Ce per Minute	Basal Meta-bolic Rate, %	Arterio-venous Oxygen Differ-ence, Ce per Liter	Cardiac Output		Liters per 100 Ce of Oxygen Con-sumed	Liters per Sq M of Surface Area	Respi-ratory Quo-tient	Vital Capac-ity, Ce	Basal Pulse Rate per Minute	Blood Pressure, Mm of Mercury
				Liters per Minute	Ce per Beat						
13	203	+ 6	44.8	4.53	56.6	2.23	3.06	0.76	2,600	80	124/82
15	190	— 1	48.2	3.94	47.4	2.07	2.64	0.78	2,500	83	120/78
19	201	+ 3	49.0	4.10	51.2	2.04	2.69	0.80	2,500	80	112/76
21	183	— 6	43.0	4.26	50.7	2.33	2.78	0.84	2,200	84	122/74
24	200	+ 1	48.6	4.11	48.9	2.05	2.67	0.81	2,400	84	104/66
26	211	+ 5	47.5	4.44	49.9	2.10	2.88	0.77	2,400	89	118/72
28	203	+ 1	53.5	3.79	41.2	1.87	2.43	0.79	2,300	92	106/75
30	208	+ 4	33.5	6.20	72.1	2.93	3.97	0.81	2,600	86	
33	222	+10	52.7	4.21	54.7	1.89	2.68	0.81		77	118/80
35	222	+ 9	71.8	3.09	40.1	1.39	1.97	0.76	2,700	77	100/65
36	220	+ 9	58.6	3.76	43.7	1.71	2.38	0.84	2,600	86	115/85
37	217	+ 6	67.0	3.24	39.1	1.49	2.05	0.79	2,500	83	105/72
38	211	+ 3	53.7	3.93	46.8	1.86	2.49	0.76	2,600	84	100/72
39	206	+ 1	77.8	2.65	31.2	1.28	1.63	0.81	2,600	85	118/86
40	213	+ 5	58.3	3.65	41.5	1.71	2.29	0.85	2,500	88	125/95
Post partum											
1½	176	— 7	55.0	3.20	42.7	1.82	2.13	0.83	2,900	75	108/86
1½	175	— 9	48.4	3.61	43.8	2.63	2.40	0.84	2,900	74	110/84
9	177	— 9	51.6	3.43	47.6	1.94	2.24	0.77	2,700	72	112/80

TABLE 2—Data for K E (case 2)

Week of Preg-nancy	Oxygen Con-sump-tion, Ce per Minute	Basal Meta-bolic Rate, %	Arterio-venous Oxygen Differ-ence, Ce per Liter	Cardiac Output		Liters per 100 Ce of Oxygen Con-sumed	Liters per Sq M of Surface Area	Respi-ratory Quo-tient	Vital Capac-ity, Ce	Basal Pulse Rate per Minute	Blood Pressure, Mm of Mercury
				Liters per Minute	Ce per Beat						
13	176	— 6	51.5	3.42	33.2	1.95	2.31	0.86	2,900	101	110/65
16	167	—12	51.6	3.26	34.3	1.95	2.17	0.84	2,900	95	108/65
19	176	— 9	49.0	3.59	35.9	2.04	2.38	0.80	2,900	100	100/60
21	178	— 9	41.5	4.30	46.7	2.41	2.83	0.80	2,800	92	110/60
23	174	—12	33.7	5.18	48.4	2.96	3.36	0.80	2,900	107	103/68
26	189	— 6	57.3	3.29	33.2	1.74	2.08	0.87	3,000	99	114/62
29	191	— 7	34.3	5.53	55.3	2.91	3.45	0.83	3,000	100	110/70
31	186	— 7	29.9	6.22	57.7	3.34	3.86	0.91	3,000	106	110/61
33	188	— 8	31.3	6.00	57.8	3.18	3.70	0.86	2,900	104	98/56
36	201	— 3	37.4	5.38	56.0	2.68	3.32	0.81	2,900	96	112/72
38	204	— 5	53.2	3.83	43.4	1.87	2.33	0.79	2,800	88	122/68
Post partum											
1½	153	—25	49.8	3.07	34.9	2.00	1.93	0.82	2,800	88	118/62
5½	138	—28	52.3	2.64	36.6	1.91	1.76	0.83	2,900	72	95/65
32	153	—20	51.7	2.96	37.0	1.94	1.98	0.84	3,000	80	112/70

TABLE 3—Data for L F (case 3)

Week of Preg-nancy	Oxygen Con-sump-tion, Ce per Minute	Basal Meta-bolic Rate, %	Arterio-venous Oxygen Differ-ence, Ce per Liter	Cardiac Output		Liters per 100 Ce of Oxygen Con-sumed	Liters per Sq M of Surface Area	Respi-ratory Quo-tient	Vital Capac-ity, Ce	Basal Pulse Rate per Minute	Blood Pressure, Mm of Mercury
				Liters per Minute	Ce per Beat						
12	164	—15	46.2	3.55	47.3	2.16	2.37	0.78	2,800	75	108/74
15	163	—14	43.1	3.90	51.3	2.32	2.57	0.78	2,600	76	104/66
17	159	—19	40.5	3.92	51.6	2.46	2.56	0.79	2,600	76	114/64
22	177	—13	30.7	5.77	76.9	3.27	3.65	0.81	2,600	75	106/66
24	192	— 6	32.2	5.96	73.6	3.11	3.77	0.79	2,700	81	126/70
27	185	— 9	35.7	5.18	64.7	2.80	3.24	0.82	2,600	80	115/62
29	195	— 4	37.1	5.25	52.0	2.69	3.28	0.86	2,500	101	110/60
32	191	— 6	37.8	5.05	50.5	2.64	3.14	0.83	2,400	100	108/60
36	214	+ 3	54.0	3.96	40.0	1.85	2.44	0.80	2,700	86	110/70
37	213	+ 2	42.8	4.97	59.2	2.33	3.03	0.83	2,700	84	113/63
38	201	— 3	52.2	3.85	44.2	1.92	2.36	0.83	2,700	87	110/80
39	200	— 3	44.0	4.55	50.5	2.27	2.81	0.84	2,600	90	113/74
Post partum											
2	163	—16	49.1	3.32	56.3	2.04	2.21	0.77	2,700	59	110/80
7	158	—19	44.4	3.56	49.4	2.25	2.34	0.81	2,500	72	112/80

TABLE 4—Data for *M W* (case 4)

Week of Pregnancy	Oxygen Consumption, Cc per Minute	Basal Metabolic Rate, %	Arterio-venous Oxygen Difference, Cc per Liter	Cardiac Output		Liters per 100 Cc of Oxygen Consumed	Liters per Sq M of Surface Area	Respiratory Quotient	Vital Capacity, Cc	Basal Pulse Rate per Minute	Blood Pressure, Mm of Mercury
				Liters per Minute	Cc per Beat						
23	211	+0	33.4	6.32	74.2	3.00	3.68	0.99	3,700	85	115/65
28	207	-7	33.8	6.12	72.8	2.95	3.52	0.81	4,100	84	130/76
31	207	-9	37.5	5.52	69.0	2.67	3.10	0.83	4,100	80	120/66
33	225	-5	39.1	5.75	71.8	2.56	3.16	0.77	3,900	80	110/70
39	229	-1	48.9	4.68	57.8	2.04	2.59	0.80	4,100	80	115/80
40	234	+1	50.8	4.61	57.6	1.97	2.55	0.81	4,200	80	126/86
Post partum											
1½	220	-4	51.5	4.27	44.0	1.94	2.40	0.81		97	128/85
1½	217	-4	52.5	4.13	46.9	1.90	2.32	0.85		88	126/80

TABLE 5—Basal Heart Rate During and After Pregnancy*

Case	During Pregnancy	After Pregnancy
1	86	74
2	98	80
3	94	66
4	82	93

* The average of all counts is recorded

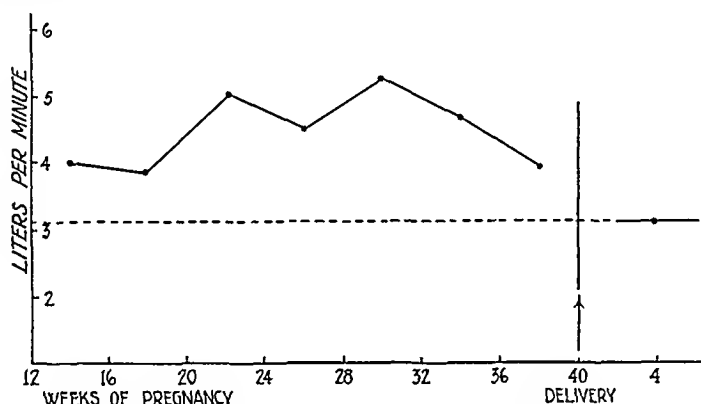


Fig. 3—The cardiac output in the fourth to the tenth month of pregnancy and in the puerperium

partum, at which time lactation was causing discomfort¹⁵ The average of all counts for all 4 patients is charted by months in figure 1. In addition to the investigation of these patients, records of the pulse rates of 13 patients during the performance of abdominal cesarean section have been studied. In 7, in spite of many influences which might have operated to increase the pulse rate, there was a critical drop of 10 beats per minute or more when the placental circulation was interrupted.

¹⁵ This patient's heart was reexamined under basal conditions on March 1, 1938, by one of us (Dr Strayhorn). This was several years after the observations recorded in table 4. After thirty minutes of rest her blood pressure was 134 systolic and 85 diastolic, her basal metabolic rate —5 per cent and her pulse rate 76. This rate was definitely lower than the average she exhibited under similar conditions during pregnancy.

The Blood Pressures—The arterial blood pressure under standard conditions showed significant changes during pregnancy (fig 2) In comparison with pressures observed post partum, the diastolic pressure manifested during pregnancy a greater fall than the systolic, so that

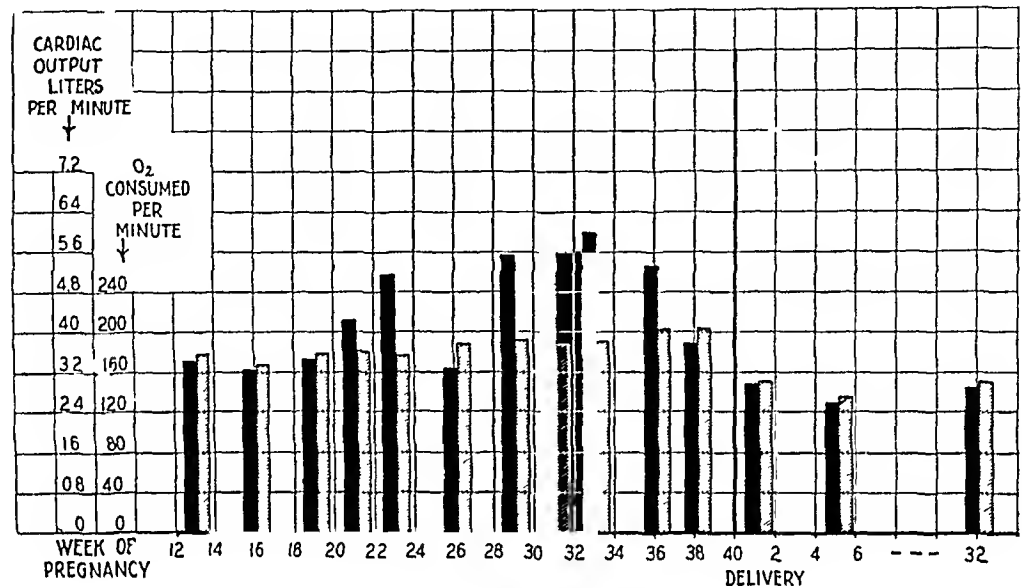


Fig 4—The cardiac output (solid columns) and the total oxygen consumption (barred columns) during pregnancy and the puerperium

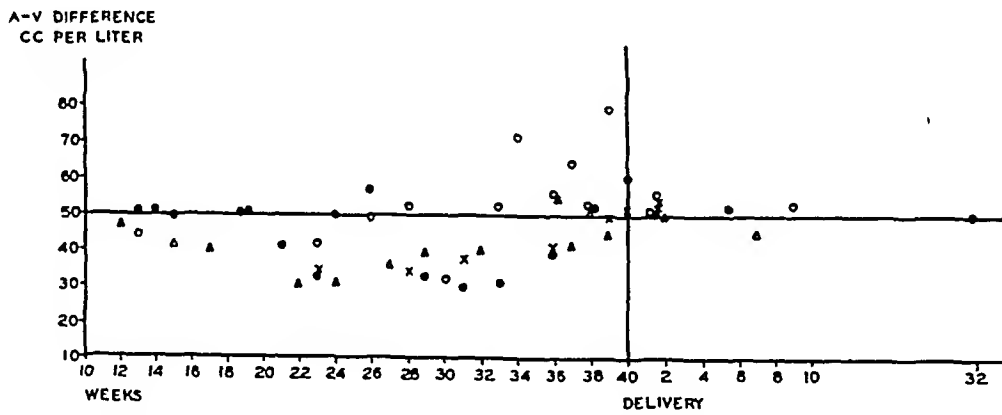


Fig 5—Arteriovenous differences in 4 women during pregnancy and the puerperium In this figure the horizontal line at 50 cc per liter indicates the approximate lower limit for the arteriovenous difference in normal nonpregnant women The hollow circles represent the values obtained in case 1, the solid circles, those obtained in case 2, the triangles, those obtained in case 3, and the crosses, those obtained in case 4

the pulse pressure rose A similar change was observed in a larger group of patients by Landt and Benjamin¹⁶

16 Landt, H, and Benjamin, J E Cardiodynamic and Electrocardiographic Changes in Normal Pregnancy, Am Heart J 12 592, 1936

The Cardiac Output—The cardiac output during pregnancy, knowledge of which was the first object of these investigations, showed several significant changes. Figure 3 represents graphically the average cardiac output for each month of pregnancy from the fourth onward and for some months of the puerperium, the figures for all 4 of our subjects being utilized. This curve shows an elevation beginning about the fifth month of pregnancy, a variable but persistently high level through the sixth, seventh, eighth and ninth months and a fall toward (but not to) the average level for nonpregnant women during the last month of pregnancy.

In figure 4 the heights of the black columns indicate the individual measurements of cardiac output for 1 patient, these outputs show, in general, the same trend as the averages. This figure also illustrates another point of importance. The cardiac output is charted against the oxygen consumption, and it is strikingly apparent that the output of the heart was increased far out of proportion to the rise in oxygen con-

TABLE 6—*The Arteriovenous Oxygen Difference in Successive Periods of Pregnancy*

Case	26th to 35th Week, Cc per Liter	36th to 40th Week, Cc per Liter
1	51.8	63.1
2	38.2	45.8
3	36.8	48.2
4	35.4	46.3
Average	40.5	50.9

sumption. A similar relation was found in the other subjects. Such a disproportionate increase implies a diminution in the arteriovenous difference or oxygen utilization. Figure 5 is a chart showing the arteriovenous difference at each determination for all patients throughout the period of observation. For each patient there was a fall in the arteriovenous difference during the period of highest output, and there was a rise toward normal in the last weeks of pregnancy. That this rise was a real event is indicated in table 6, where it appears that the average arteriovenous difference from the twenty-sixth to the thirty-fifth week of pregnancy was 40.5 cc per liter, while from the thirty-sixth to the fortieth week it was 50.9 cc per liter.

The fetus increases rapidly in size and weight during the last weeks of pregnancy, and the oxygen consumption of the mother continues its gradual rise (fig. 6). Nevertheless, the total cardiac output of the mother falls during this period. This fall in output was first observed by Lindhard,² who ascribed it to relative physical inactivity on the part of the mother. It appeared in each of our 4 patients, all of whom continued to be active during the period when the low output was observed.

It was not synchronous with "lightening" but did occur at about the period of pregnancy when changes in the protein content of the plasma¹⁷ indicate that concentration of the blood occurs. Our own observations offer no explanation of this phenomenon, but some recent studies of the circulating blood volume during pregnancy in normal women by Thom-

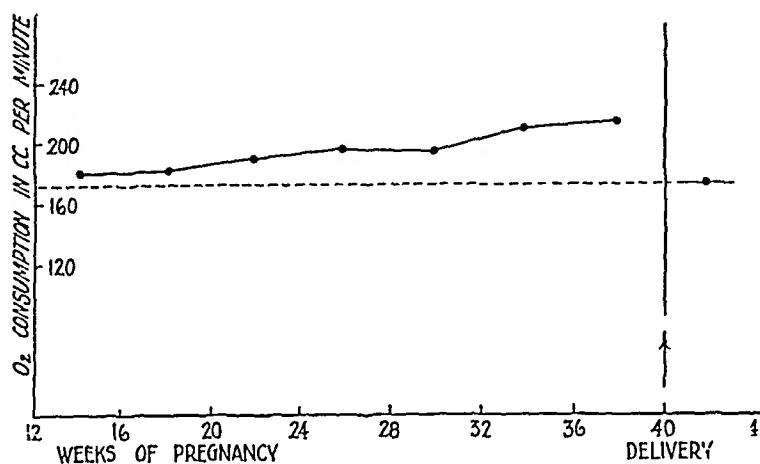


Fig 6—The oxygen consumption in the fourth to the tenth month of pregnancy and in the puerperium



Fig 7—The blood volumes in the fifth to the tenth month of pregnancy and in the puerperium, drawn from the data of Thomson, Hirsheimer, Gibson and Evans¹⁸

son, Hirsheimer, Gibson and Evans¹⁸ may bear on the problem. These observers, using the method of Gibson and Evans,¹⁹ studied 15 normal

17 Plass, E D, and Bogert, L J. Plasma Protein Variations in Normal and Toxemic Pregnancies, *Bull Johns Hopkins Hosp* **35** 361, 1924

18 Thomson, K J, Hirsheimer, A, Gibson, J G, II, and Evans, W A, Jr. Studies on the Circulation of Pregnancy. III. Blood Volume Changes in Normal Pregnant Women, *Am J Obst & Gynec* **36** 48, 1938

19 Gibson, J G, II, and Evans, W A, Jr. Clinical Studies of the Blood Volume. I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, *J Clin Investigation* **16** 301, 1937

women, making repeated determinations during pregnancy. The average increase in total blood volume during pregnancy was 42 per cent, and there was a fall toward the normal level during the last weeks of pregnancy. In general, their curves for the volumes are similar to our curves for the output, as is shown in figure 7, which is based on data which these authors have generously permitted us to use in this way. This shrinkage in the amount of fluid filling the vascular system may be a factor in the otherwise unexplained diminution of cardiac output during the last weeks of pregnancy.

Our observations concerning the cardiac output, even to the fall during the last weeks, are not out of harmony with the results of the careful studies of Cohen and Thomson²⁰ concerning the velocity of blood flow during pregnancy.

Our records of the vital capacity showed only minor fluctuations during pregnancy. Thomson and Cohen,²¹ in their study of a large number of patients, found that the vital capacity remained constant or increased slightly. The absence of striking diminution in the vital capacity is worthy of note, since it indicates that any marked alteration in this function is not to be dismissed as due to the pregnancy itself but may, on the other hand, be a relatively early sign of congestive heart failure.

SUMMARY

Observations on the pulse rate, the systemic blood pressure, the vital capacity, the arteriovenous difference and the cardiac output were made for 4 women during the course of pregnancy and in the puerperium. These primary observations may be summarized as follows:

- 1 The basal pulse rate is higher during pregnancy than after delivery, the basal blood pressure (particularly the diastolic phase) is lower during pregnancy than after its termination.

- 2 The cardiac output is increased, by as much as 50 per cent or even more, during the period of maximum increase. This increase is usually demonstrable by the third or fourth month. In the last weeks of pregnancy there is a fall in the cardiac output toward normal, and after delivery it is within the limits usual for nonpregnant women.

- 3 The increase in output is greater in proportion than the increase in oxygen consumption, therefore the arteriovenous oxygen difference is diminished.

20 Cohen, M. E., and Thomson, K. J. Studies on the Circulation in Pregnancy. I. The Velocity of Blood Flow and Related Aspects of the Circulation in Normal Pregnant Women, *J. Clin. Investigation* **15**: 607, 1936.

21 Thomson, K. J., and Cohen, M. E. Studies on the Circulation in Pregnancy. II. Vital Capacity Observations in Normal Pregnant Women, *Surg., Gynec. & Obst.* **66**: 591, 1938.

II THE PHYSICAL SIGNS IN THE CIRCULATORY SYSTEM

During pregnancy most of the patients exhibited certain physical signs which were not present post partum. These included a forceful apex beat, loud heart sounds and systolic murmurs. These signs are comparable to those observed in patients with thyrotoxicosis or severe anemia, when they are also associated with an increased cardiac output. The heart of the pregnant woman is displaced upward and lies more

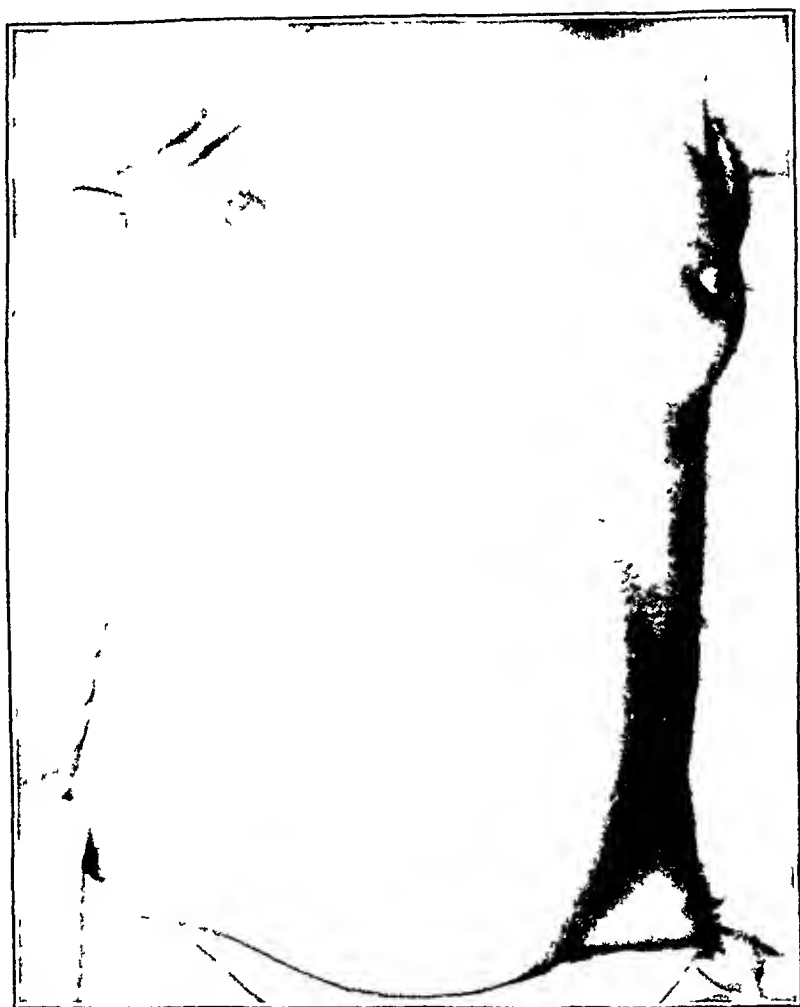


Fig 8—Infra-red photograph of the abdomen of a pregnant woman, showing the distribution of superficial veins

horizontally than usual. The abdomen is distended, but its wall is not tense. A bruit is audible over the uterus. When well heard, this is a continuous murmur with systolic accentuation. The veins of the legs are distended, the veins of the neck may also appear prominent and a network of veins may be seen over the abdomen. Figure 8, from a photograph on a plate sensitive to infra-red rays, indicates the extent of this network. Its distribution resembles that observed when collateral circulation develops after interference with free flow through the inferior vena cava.

After delivery the heart rate diminishes, the murmurs disappear or diminish, the bruit is no longer heard, the heart assumes its usual position and the veins return to their usual degree of filling and visibility

III THE VENOUS PRESSURE IN ARM AND LEG

The observations, referred to in part II, of changes in the number and the prominence of visible veins prompted a study of the pressure existing in various portions of the venous system of pregnant women. Part of the material relating to these studies has been published by one of us ²²

The first observations on this point which were discovered in the literature were those of Runge,²³ published in 1924. Runge measured the venous pressure in the antecubital vein and compared it to the pressure in the veins about the knee. In nonpregnant women without cardiac disease these pressures were approximately equal. In a number of pregnant women he observed that even early in pregnancy the pressure in the veins of the knee was considerably higher than that in the veins of the arm. He made a few observations on women with abdominal tumors and failed to find a comparable elevation. Accordingly, he concluded that the elevation of the venous pressure in the legs of pregnant women is due to the large amount of blood which flows into the venous channels about the pelvis rather than to any obstruction to the return of blood by the gravid uterus. Some observations of pressures in the arms and legs under various circumstances have been published recently by Ferris and Wilkins ²⁴

METHODS

The venous pressure in our study was determined by the method of Moritz and von Tabora,²⁵ the side arm syringe being used, as suggested by Griffith, Chamberlain and Kitchell ²⁶. The level of the right auricle was taken arbitrarily as 5 cm dorsal to the fourth costosternal junction, and this level was the zero point for all manometers. All observations were made with the patient lying flat on her back. The venous pressures were determined in the antecubital and femoral veins. The location of the femoral vein was determined by its relation to the femoral artery,

22 Burwell, C. S. A Comparison of the Pressures in Arm Veins and Femoral Veins, with Special Reference to the Changes During Pregnancy, *Ann Int Med* **11** 1305, 1938

23 Runge, H. Ueber den Venendruck in Schwangerschaft, Geburt, und Wochenbett, *Arch f Gynak* **122** 142, 1924

24 Ferris, E. B., Jr., and Wilkins, R. W. The Clinical Value of Comparative Measurements of the Pressure in the Femoral and Cubital Veins, *Am Heart J* **13** 431, 1937

25 Moritz, F., and von Tabora, D. Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch f klin Med* **98** 475, 1910

26 Griffith, G. C., Chamberlain, C. T., and Kitchell, J. R. A Simplified Apparatus for Direct Venous Pressure Determination Modified from Moritz and von Tabora, *Am J M Sc* **187** 371 1934

and in most patients no difficulty was encountered in entering it. The sites of venipuncture were anesthetized with procaine hydrochloride.

RESULTS

Since few similar studies on venous pressure have been made, it was necessary to study the relation between the venous pressures in

TABLE 7—*The Venous Pressure in Arm and Leg*

Condition of Patient		Venous Pressure, Mm of Water	
		Arm	Leg
<i>A Normal circulatory system</i>			
1	Psychoneurosis	74	64
2	Psychoneurosis	58	58
3	Obesity	72	90
4	Ulcer of duodenum	60	88
		48	48
5	Hysteria	161	141
<i>B Heart disease</i>			
(a) Without failure			
6	Hypertension (blood pressure 210/110)	42	41
	(blood pressure 212/140)	48	55
7	Mitral stenosis	75	72
8	Arteriosclerosis	76	84
(b) With failure and without ascites			
9	Hypertension	182	178
(c) With failure and with ascites			
10	Aortic regurgitation and hypertension	238	269
(d) Pericardial obstruction			
11	Constrictive pericarditis	320	304
12	Constrictive pericarditis	200	204
13	Pericardial effusion	165	167
<i>C Mediastinal tumor</i>			
14	Lymphoma of superior mediastinum	360	60
<i>D Abdominal tumor</i>			
15	Ovarian cyst (25 cm in diameter)	167	295
16	Ovarian cyst, before operation	85	153
	Ovarian cyst, after operation	112	97
17	Fibromyoma of uterus, before operation	104	274
	Fibromyoma of uterus, after operation	66	55
<i>E Ascites not due to heart disease</i>			
18	Cirrhosis	170	230
	Cirrhosis, after removal of 16,500 cc	60	55
19	Cirrhosis	105	146
	Cirrhosis, after removal of 5,000 cc	88	88

the arm and leg of nonpregnant women, including those with certain conditions which are known to affect venous pressure locally or generally.

Table 7 presents the results for several groups of patients. These figures indicate that in persons without heart disease or local venous obstruction, the venous pressures when measured under the conditions mentioned, with the subject in bed, are of the same general magnitude in the arm and in the leg. When a difference occurs it is usually the case that the pressure in the leg is higher, a point that requires further study. In patients with heart disease but without congestive failure or peri-

cardial obstruction, the venous pressures are similar in the arm and in the leg and are not elevated. In patients with manifest congestive failure and in those with pericardial obstruction due to either scar or fluid, the pressure is elevated. The amount of elevation in such cases is of the same general order in the arm and in the leg unless considerable accumulation of fluid occurs in the abdomen. When ascites is present, the pressure in the leg may be higher than that in the arm.

When obstruction to venous flow is not central²⁷ but at some peripheral point, the venous pressure may be altered locally and may

TABLE 8—*Pressure in the Veins in Arm and Leg of Women During and After Pregnancy*

Case	Months of Pregnancy	Venous Pressure, Mm of Water		Time After Delivery	Venous Pressure, Mm of Water	
		Arm	Leg		Arm	Leg
1	3	53	78	6 months	65	70
2	3½	77	100	Unknown	108	97
	8½	56	240			
3	4	102	163	5 months		118
4	6½	85	154			
	7½	98	175			
5	7	156	203			
6	7	102	232			
7	7½	80	145			
8	8	110	201	5 months		102
9	8	78	161	4 months	108	92
10	8	102	236	10 days	108	72
11	8	76	200			
12	8	110	215			
13	8	90	170	6 months	30	30
14	8½	51	183	6 months	89	81
15	8½	145	181	7 days	91	87
16	8½	95	220	1 month	110	85
17	8½	138	190	6 weeks	118	97
18	8½	82	188	6 days	162	63
19	9	62	265			
20	Near term	55	178			
21	At term	78	198			
22	At term	82	210			
23				17 days	48	55

differ widely in the arm and in the leg. Examples are given of a case of mediastinal tumor in which the pressure in the arm was higher than that in the leg and cases of intra-abdominal tumor and of large ascites in which the pressure in the leg was higher than that in the arm. In 1 patient with Laennec's cirrhosis and large ascites (16 liters was removed by paracentesis), the pressure in the arm was elevated to 170 mm, while that in the leg was 250 mm. After the paracentesis these pressures were reduced to 60 and 55 mm, respectively. It is presumably under

²⁷ Central obstruction is exemplified by failure of the right ventricle or obstructing pericardial disease.

such conditions, i. e., a higher venous pressure in one area of the body than in another, that evidence of collateral circulation may develop

With these observations in mind, we may proceed to a consideration of the venous pressures in the arms and legs of pregnant women. Table 8 records 24 observations for 22 women, figure 9 presents the same material graphically. It is seen that by the beginning of the second trimester of pregnancy there is a rise in the venous pressure of the leg and that this elevation persists and even increases throughout pregnancy. It may be added that in 1 woman, who was observed repeatedly during the last two weeks of pregnancy, the venous pressure remained high until delivery and then fell abruptly to normal. There was no change in the curve of femoral pressure comparable to that

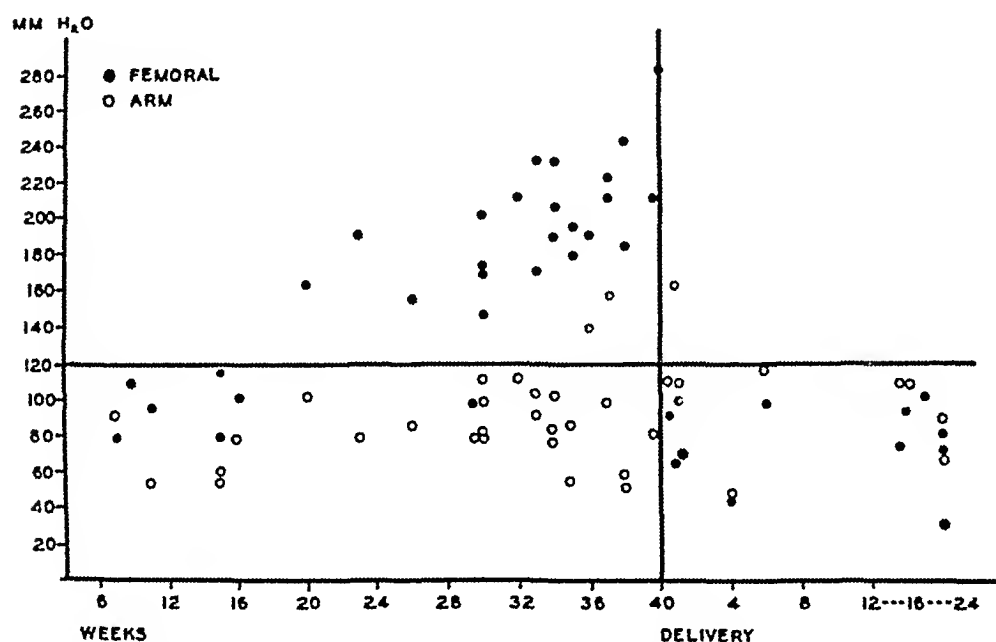


Fig 9—The pressure in the femoral vein and in a vein of the arm during pregnancy and the puerperium

observed in the curve of the cardiac output in the last weeks of pregnancy

The factors which may cause changes in the pressure in the femoral vein in nonpregnant persons are many. These factors include ascites or other causes of increased intra-abdominal pressure as well as pressure from adjacent structures on intra-abdominal veins. Further work is required to identify and evaluate these factors. The point at issue here, however, seems clear, viz, there is during pregnancy a significant elevation of the pressure in the femoral vein as compared with the venous pressure in the arm or with the femoral pressure in the same patient post partum.

SUMMARY

The observations on venous pressures in pregnant women may be summarized as follows

1 Venous pressures are nearly the same in the arm and in the leg in supine persons, both normal persons and patients with central obstruction, leading to general elevation of the venous pressure

2 Differences between these pressures may exist when there is a condition affecting the venous return from a part of the body, such as a mediastinal or pelvic tumor

3 In pregnant women by the beginning of the second trimester the pressure in the leg is notably higher than that in the arm. It continues high throughout pregnancy, but after delivery it is found to be no higher than the pressure in the arm

IV RELATED OBSERVATIONS FOR ANIMALS

Stander, Duncan and Sisson¹² observed in pregnant bitches an increase in cardiac output comparable to that found in pregnant women. This observation suggested the application to these animals of some of the methods applied to the study of the circulation in pregnant women. A study was made of the pressure in the jugular, femoral and uterine veins of pregnant bitches. Observations were made with the animals supine and under barbitol anesthesia. It should be emphasized that observations on pregnant animals cannot be applied directly to the problem in human beings, because of the difference in the structure of the placenta in various species. Such observations may, however, be interpreted in broad terms. The pressures observed under various circumstances are summarized in table 9.

It was observed first that the pressure in the femoral vein of the pregnant animals was higher than that in the jugular vein and that the difference was comparable to that observed between the femoral and the antecubital pressure in pregnant women. This difference between the pressures in the veins of the neck and leg was diminished or absent post partum.

When the abdomen of pregnant bitches was opened by a long incision the pressure in the femoral vein did not alter, therefore, the high venous pressure in the legs of these animals was not due to an increase in general abdominal pressure. When the gravid uterus was lifted from its normal position in the abdomen and supported so that it no longer pressed on the great veins, the pressure in the femoral vein fell but usually remained above the pressure in the jugular vein. When the uterus was removed and its vascular connections were severed, the pressure in the femoral vein approached that of the jugular vein.

After the abdomen was opened it was possible in these animals to study also the veins running in the broad ligaments and apparently draining the uterine wall and the placental sites. These were large, firm veins, in which the blood was obviously under relatively high pressure. These pressures were found to be sometimes as much as 100 mm higher than the femoral pressure in the same animal.

Further observations were made concerning the relation of general abdominal pressure and venous pressure in the leg. Dogs (nonpreg-

TABLE 9—*Venous Pressure in Jugular, Femoral and Uterine Veins of Pregnant Bitches**

Animal	Vein	Pressure, Mm. of Water			
		Initial Pressure	Abdomen Opened	Uterus Lifted Up	Uterus Removed
4	Femoral	130	130	80	30
	Uterine			130	
	Jugular	25	25	25	25
5	Femoral	120	110	105	52
	Uterine			100 140	
	Jugular	30	22	35	30
6	Femoral	118	130	75	65
	Uterine		240		
	Jugular	20	10	5	-2
8	Femoral	75	65	45	14
	Jugular	16	15	15	8
X	Femoral	143	120	85	
	Uterine			163	
	Inferior vena cava	40	40	40	
Y	Femoral	100	90	60	
	Uterine			120	
Z	Femoral		140	60	60
	Uterine		230		
9	Femoral	105	105	55	30
	Jugular	58	58	58	
11	Femoral		130	70	40
	Jugular		5	10	10
14	Femoral	140	135	90	15
	Jugular	-2	-2	-5	-10
13	Femoral, before delivery	155			
	Femoral, 10 days after delivery	65			
7	15 hours post partum				
	Femoral	60			
	Uterine	60			
	Jugular	15			

* Measurements were made with the dog, under barbital anesthesia, lying on its back. The zero points of the manometers were at the level of the apex impulse.

nant) were anesthetized and placed in the dorsal position on the table. The femoral and jugular veins and the abdominal cavity were connected to manometers filled with physiologic solution of sodium chloride. Then normal solution of sodium chloride was introduced into the abdomen through a trocar, and the effects of successive injections were observed. An example of these experiments is given in table 10. The following results were noted: 1. The venous pressure in the leg does not rise with the injection of fluid into the peritoneal cavity until the general intra-abdominal pressure begins to go up. 2. When the venous pressure in the leg and the intra-abdominal pressure (which have risen together)

reach a height comparable to the femoral pressure in pregnant animals (or women), the abdominal wall is tense. Conversely, the abdominal wall of the pregnant bitch or pregnant woman is not tense even though the femoral pressure is high. 3 The jugular pressure may rise slightly

TABLE 10—*Venous Pressure in Femoral and Jugular Veins in Relation to Elevated Abdominal Pressure in Dogs**

Experiment No	Cc of Saline Solution Injected into Peritoneal Cavity	Pressure, Mm. of Water		
		Intra Abdominal	Femoral Vein	Jugular Vein
1	0		35	
	1,170	55	56	
	1,600	82	82	
	2,000	110	109	
	2,400	155	161	
	3,000	212	212	
2	0		12	22
	1,350	75	80	10
	1,590	85	75	11
	2,190	135		23
	2,590	185		23
	2,890	270		30
	3,040	310	320	45
	3,190	355	360	45
3	0		12	22
	2,800	130	146	30
	3,200	205	220	28
	3,600	300	310	23
	4,200	400	405	32
	4,700	565	575	35
	4,700	650	660	35
4	0		— 2	— 1
	300		+ 6	— 3
	800	+ 20	+ 37	— 2
	1,400	+ 60	+ 72	± 0
	2,000	+145	+148	— 1
	2,600	270	270	— 1
	2,800	345	342	+ 2
	3,000	410	410	+ 4
	3,200	490	495	+11
	3,300	525	525	+12
	All fluid removed from abdomen		0	+ 8

* The scales were set so that the zero point was at the level of the apex beat

TABLE 11—*Comparison of Oxygen Content of Blood Drawn from Arteries, Uterine Veins and Right Side of Heart in Pregnant Bitches*

Dog	Oxygen Content, Vol %		
	Blood from Right Side of Heart	Blood from Uterine Vein	Arterial Blood
X	8.77	9.44	13.60
14	6.30	7.50	9.10
15	11.28	12.48	15.96
H1	10.81	9.68	17.64
		12.17	
		15.07	

when a large amount of fluid has been injected into the abdomen and the abdominal pressure is high

Blood was taken from a small number of the distended veins near the placenta, and the oxygen content was determined. Table 11 indicates that blood from the veins draining the uterus and placenta usually contains more oxygen than does blood from the right ventricle (mixed

venous blood), i. e., the arteriovenous difference in blood from this area is small. Dog H1 also showed that there may be considerable variation in the oxygen saturation of maternal blood leaving the uterus. Barcroft,²⁸ in more extensive observations on pregnant rabbits, observed that early in pregnancy there was a relatively high oxygen saturation of the blood leaving the placental site. As pregnancy advanced the oxygen saturation of this blood diminished, and just before delivery it was low. Barcroft also pointed out that in a number of other animals the saturation of the blood going to the fetus is higher than that of normal mixed venous blood. The variation in the tension observed by us may be due to the stage of pregnancy (not always known) or to the obvious difficulty of being sure that a given vein is actually draining the placenta.

SUMMARY

These observations on animals may be summarized as follows:

1. Pressure in the femoral veins is elevated during pregnancy, that in the uterine veins is higher than that in the femoral veins.
2. These changes are not due to an increase in general intra-abdominal pressure.
3. The femoral pressure may be lowered if the uterus is elevated and supported, it may be further lowered if the uterus is excised and its vascular connections are severed.
4. Blood from the veins draining the pregnant uterus tends to exhibit an oxygen content that is high in relation to that of the blood in the right ventricle.

V. MECHANISMS OF THE CHANGES IN THE CIRCULATION DURING PREGNANCY

The chief alterations observed in the maternal circulation during pregnancy are as follows: (1) an increase in the total cardiac output per minute, (2) a decrease in the arteriovenous difference, (3) a rise in the pressure in certain veins, (4) a loud murmur over the placenta and (5) an increase in pulse rate and pulse pressure. To these observations of our own may be added those of Thomson and his colleagues, already referred to, concerning an increase in the total blood volume. An acceptable understanding of the underlying mechanisms should offer a general explanation of these phenomena.

We may consider first the mechanisms concerned with the elevation of venous pressure in the legs. The pressure exerted by the blood in any vein is dependent partly on the resistance to its outflow and partly on the amount and the pressure of the blood flowing in. Comparison with data for patients with a solid or cystic tumor of the pelvis sug-

²⁸ Barcroft, J. Fetal Circulation and Respiration, *Physiol. Rev.* **16**:103, 1936.

gests that an important factor in the rise of venous pressure is interference with venous flow by the pressure of the enlarging uterus. Certain considerations, however, lead us to inquire whether the factor of increased flow into the venous reservoir, a factor considered by Runge of prime importance, is not also operative. These considerations include the extent of the elevation of the pressure in the uterine veins as compared with that in the femoral veins and the size and the number of the uterine vessels. These vessels are obviously capable of transporting a large volume of blood per minute. Moreover, the observations on pregnant animals concerning the effects of changing the position of the uterus suggest that the factor of obstruction is not the only one. It may be concluded that there are two factors concerned with the high pressures in the femoral veins: (1) obstruction by the enlarging uterus and (2) increased flow into the veins of the region.

The striking changes in the quantitative aspects of blood flow are now to be considered. In pregnancy one is dealing with a parasitic organism (the fetus) which requires the benefits of blood supply. Moreover, as Barcroft has pointed out, this organism is not irrigated directly with maternal blood but carries on its gaseous metabolism by a relatively inefficient "relay." It is therefore to be expected that a large volume of maternal blood should flow through the placenta per unit of time.

In such an intricate series of events as those of the pregnant state, there may be many influences playing on the circulation. Among the other factors which have been thought to influence the circulation during pregnancy, the activity of the maternal thyroid gland is to be considered. The present evidence appears to indicate that increased thyroid function is at most only a minor factor in the circulatory changes of normal pregnancy.

When one considers the changes in circulation other than those associated with the obstruction, it is apparent that they are in many respects similar to the changes observed in the circulation of patients with a large arteriovenous connection or a fistula.

Alterations in the circulation of patients with an arteriovenous connection have been studied by Halsted,²⁹ Reid,³⁰ Lewis and Drury,³¹

29 Halsted, W. S. Congenital Arterio-Venous and Lymphatico-Venous Fistulae. Unique Clinical and Experimental Observation, *Proc Nat Acad Sc* **5** 76, 1919.

30 Reid, M. R. The Effect of Arteriovenous Fistula upon the Heart and Blood Vessels, *Bull Johns Hopkins Hosp* **31** 43, 1920.

31 Lewis, T., and Drury, A. N. Observations Relating to Arterio-Venous Aneurism. I. Circulatory Manifestations in Clinical Cases with Particular Reference to the Arterial Phenomena of Aortic Regurgitation, II. Immediate Effects of an Arterio-Venous Anastomosis on the Dog's Circulation, *Heart* **10** 301, 1923.

Harrison, Dock and Holman,³² Matas,³³ Brown,³⁴ Ellis and Weiss,³⁵ Smith,³⁶ Laplace,³⁷ Kennedy and Burwell,³⁸ and others. Such patients may exhibit (1) tachycardia, (2) an increased pulse pressure (which may be associated with peripheral signs comparable to those in patients with aortic regurgitation), (3) an increase in the cardiac output per minute, (4) a decrease in the arteriovenous oxygen difference (because the cardiac output is increased more than the oxygen consumption), (5) a continuous bruit, with systolic accentuation, heard in the region of the fistula, (6) an elevated pressure in the veins adjacent to the fistula, (7) a higher oxygen saturation of the blood in such veins than in the mixed venous blood, and (8) an increase in the total blood volume. Each of these phenomena has been shown by the observations here reported or quoted to be present in pregnant women, although not always in as marked degree as in patients with an arteriovenous fistula. These similarities suggest that one of the mechanisms concerned with the circulatory changes in the pregnant woman is an arteriovenous shunt similar to that which exists in an arteriovenous fistula. It is true that the changes in the pulse (collapsing pulse and increased pulse pressure) are less marked in the pregnant woman than in patients with a large direct arteriovenous connection, but they are present, and the other manifestations occur in the two conditions in striking parallelism.

It is now necessary to consider whether the structure of the human placenta is compatible with the hypothesis that an arteriovenous shunt occurs within it. An instructive and recent description of the vascular system of the placenta is that of Spanner.³⁹ In this admirable treatise he has pointed out that in the placenta relatively large arteries connect with relatively large veins through large vascular spaces and without the interposition of arterioles or capillaries. Several hundred arteries (about 500), with a terminal diameter averaging 0.15 mm, empty directly

32 Harrison, T. R., Dock, W., and Holman, E. Experimental Studies in Arterio-Venous Fistulae. Cardiac Output, Heart **11** 337, 1924.

33 Matas, R. On the Systemic or Cardiovascular Effects of Arteriovenous Fistulae, Internat Clin **2** 58, 1925.

34 Brown, G. E. Abnormal Arteriovenous Communications Diagnosed from the Oxygen Content of the Blood of Regional Veins, Arch Surg **18** 807 (March) 1929.

35 Ellis, L. B., and Weiss, S. The Local and Systemic Effects of Arterio-Venous Fistula on the Circulation in Man, Am Heart J **5** 635, 1929.

36 Smith, C. Circulation in Arteriovenous Aneurysm Before and After Operation, Arch Int Med **48** 187 (Aug.) 1931.

37 Laplace, L. B. Observations on the Effect of an Arteriovenous Fistula on the Human Circulation, Am J M Sc **189** 497, 1935.

38 Kennedy, J. A., and Burwell, C. S. Venous Pressures, Cardiac Output and Blood Volume in Arteriovenous Fistula, J Clin Investigation **16** 671, 1937.

39 Spanner, R. Mutterlicher und kindlicher Kreislauf der menschlichen Placenta und Strombahnen, Ztschr f Anat u Entwicklungsgesch **105** 163, 1936.

(like the nozzles of garden hose) into the intervillous space. An illustration of these arteries, taken by permission from Spanner's article, is shown in figure 10. This figure not only shows the artery and the manner of its termination in the intervillous space but also presents another finding of great interest. It was pointed out by Halsted²⁹ that in the case of an arteriovenous fistula, the artery dilates proximal to the point of leakage into the area of lower pressure. The arteries in the

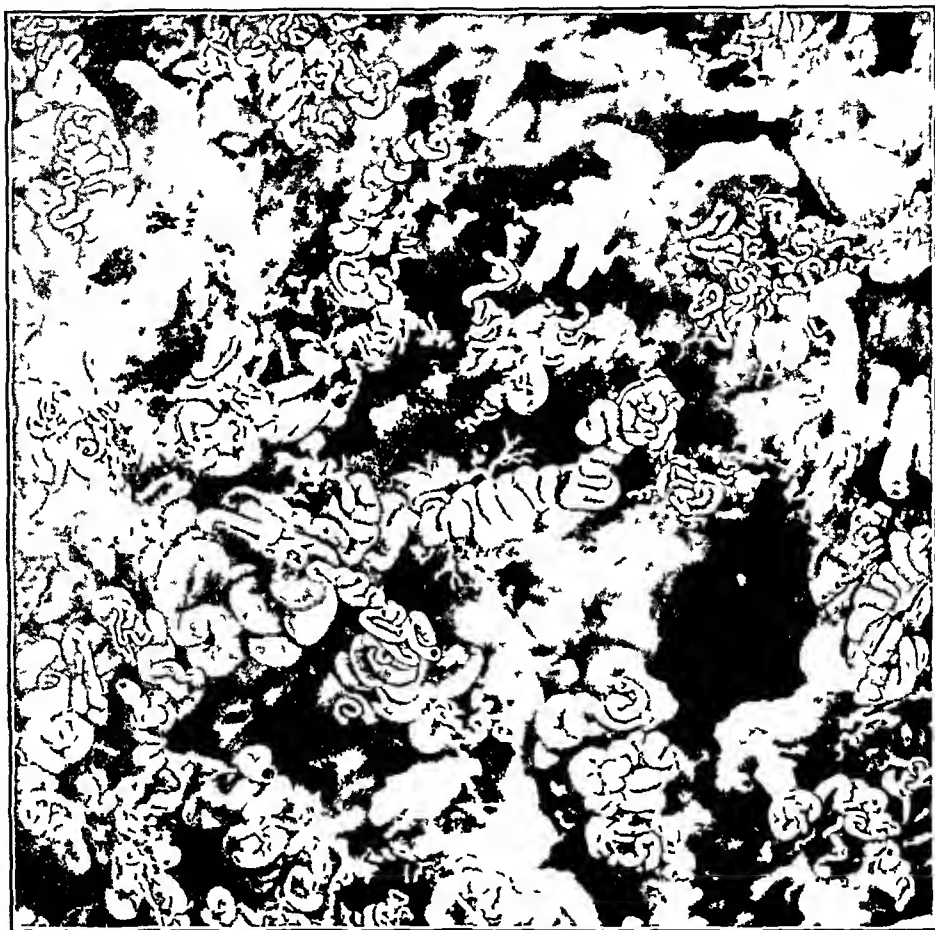


Fig 10—Terminal arteries of the placenta emptying into the intervillous space (from Spanner)

placenta which empty into the intervillous space also are dilated for a short distance proximal to the point of emptying.

According to Spanner, blood escapes from the intervillous space by flowing into the marginal sinus through relatively wide openings. The structure of the maternal vascular system in the placenta thus offers a connection between arteries and veins which has both similarities to and differences from a simple arteriovenous shunt. The similarities have been pointed out. The differences, in the main, are two. First, between artery and vein there are interposed the tortuous channels of the inter-

villous space, and these channels are filled with blood. Second, some of the venous blood flowing from the placenta enters a venous reservoir in which the pressure is already high because of the obstruction offered by the uterus to the venous return from the legs and the pelvic region. It is possible to conceive that these two factors may influence the manner and the extent of the leakage of blood and pressure through the placenta and therefore the degree to which the circulation of the pregnant woman presents the changes characteristic of the presence of an arteriovenous fistula.

The changes in both the pregnant woman and the patient with an arteriovenous fistula may be shown by the application of an appropriate formula (e. g., Bainbridge's⁴⁰) to increase the work of the heart. This increased burden is continuous, like that in cases of valvular disease or thyrotoxicosis, and is not discontinuous, like that brought about by physical exertion. Its importance in patients with heart disease is obvious. The disadvantages of the increase in venous pressure in the legs are also obvious in their relation to edema and varicosities.

SUMMARY AND CONCLUSIONS

The chief alterations in the circulation of pregnant women are as follows:

- 1 An increased cardiac output per minute
- 2 A decrease in the arteriovenous difference
- 3 A rise in the pressure in the veins of the lower extremities
- 4 An increase in pulse rate and pulse pressure
- 5 A loud bruit over the site of the placenta
- 6 An increase in total blood volume

The demonstrated phenomena of the circulation in pregnant women and pregnant animals, plus the available knowledge concerning the structure of the placenta, lead to the conclusion that the changes in the circulation during pregnancy are in the main to be ascribed to two mechanisms: (1) an arteriovenous leak through the placenta and (2) an obstruction to venous return by the enlarged uterus.

⁴⁰ Bainbridge, F. A. *The Physiology of Muscular Exercise*, ed. 3, London, Longmans, Green & Co., 1931.

THALASSANEMIA

REPORT OF A CASE

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Thalassanemia is a rare disease in Montreal. The following case is the first and only one reported from the wards of three of the largest hospitals in this city, which in 1937 had an estimated population of 885,000, of which 25,514 were Greeks, Syrians and Italians. The case is of further interest in that the character of the cutaneous pigmentation and the changes in the blood and bone marrow diverged somewhat from those recorded in classic descriptions of the disease.

REPORT OF CASE

The patient, a girl aged 13 months, of Greek parentage, was admitted to the Children's Memorial Hospital on July 13, 1936, because of an infection of the upper respiratory tract and vomiting of one week's duration. The parents stated that the yellowness of the skin had been present since one month after birth. The food had consisted almost entirely of modified cow's milk.

Two of the child's brothers had died after a prolonged illness characterized by slight icterus and anemia. Five other children in the family were alive and well.

Physical Examination—Physical examination on entry showed that the child was underdeveloped and undernourished and was unable to sit up. She was the size of an 8 month old baby. The skin was yellowish brown, the pigmentation being evenly distributed over the entire body. The conjunctivas were swollen and pale and the scleras pearly blue. The heart was considerably enlarged both to the right and to the left but was free from murmurs. The liver extended 4 fingerbreadths and the spleen 2 fingerbreadths below the costal margin. There was no epiphyseal flaring or other evidence of rickets. Physical examination was otherwise unimportant.

Laboratory Examination—Urinalysis showed no albumin, casts, sugar or pigment. The urobilinogen content was normal. The Wassermann test of the blood gave a negative reaction. The Mantoux test (1:1,000) gave a negative reaction. The van den Bergh test showed 2 units of bilirubin. The value for total proteins in the blood was 5.74 per cent (albumin, 4.2 per cent, globulin, 1.4 per cent, fibrinogen, 0.14 per cent). After an Ewald meal, all fractions of the gastric contents contained free hydrochloric acid, with the maximum acidity in sixty minutes. The total acidity was 44. The blood count showed red blood cells, 810,000, hemoglobin, 15 per cent, white blood cells, 21,400, polymorphonuclears, 32 per cent, lymphocytes, 47 per cent, monocytes, 10 per cent, basophils, 1 per cent, myelocytes, 2 per cent, normoblasts, 6 per cent, and reticulocytes, 4.5 per cent. The platelet count was 208,000. Smears showed marked microcytosis, with many

basochromic and stippled cells. There were rare macrocytes. The fragility test showed beginning hemolysis with 0.45 per cent solution of sodium chloride and complete hemolysis with 0.25 per cent solution. No sickle cells were present.

Roentgenograms were made of the skull, ribs and long bones. The heart was shown to be greatly enlarged in all diameters, particularly the left auricle. The roentgenograms of the skull showed indefinite thickening of the frontal and parietal bones but no ray formation. The long bones of the arms and legs had thin cortices with a somewhat expanded appearance. Ossification was normal.

Biopsy of a specimen from a rib showed a dark red, very cellular marrow with widened trabecular spaces. Histologically the predominating cell was a large immature nongranular cell with a large vesicular nucleus. Many of these cells



Fig 1—A photograph taken on July 21, 1936, when the patient was 13 months old. The protuberant abdomen is notable.

showed karyokinesis. Between these foci of immature cells were areas of normal myeloid activity, but maturing erythrocytes were relatively scarce. No foam cells were noted.

An electrocardiogram showed sinus arrhythmia, with preponderance of the right ventricle.

Course—The child showed considerable improvement as a result of repeated transfusions and general hospital care. The temperature showed a daily fluctuation between normal and 100 F. She gained in weight and strength, and her color improved. On September 18 the hemogram showed red blood cells, 2,540,000, hemoglobin, 40 per cent, reticulocytes, 9.9 per cent, white blood cells, 8,600,

polymorphonuclears, 57 per cent, lymphocytes, 39 per cent, monocytes, 2 per cent, basophils, 1 per cent, eosinophils, 1 per cent, and normoblasts, 7 per cent. No change occurred in the cardiac enlargement or in the roentgenographic appearance of the bones. She was discharged on December 14.

Second Admission to the Hospital—On Jan 15, 1937, the patient reentered the hospital because of another infection of the upper respiratory tract. In the interval she had gained in both weight and strength, although there was little change in the pigmentation of the skin or in the degree of anemia. The liver and spleen were still palpable though no larger. Cardiac enlargement was again noted.

A blood count, made on January 19, showed red blood cells, 2,050,000, hemoglobin, 32 per cent, white blood cells, 9,150, normoblasts, 4 per cent, reticulocytes, 2.9 per cent, polymorphonuclears, 51 per cent, lymphocytes, 34 per cent, eosinophils, 4 per cent, and monocytes, 11 per cent. There were 188,000 platelets. The fragility test showed beginning hemolysis with 0.375 per cent solution of sodium chloride and complete hemolysis with 0.25 per cent solution.



Fig 2—A photograph taken on June 8, 1937, when the child was 26 months old. The facies was not that of mongolism, although there was deep pigmentation.

She was discharged on February 18.

Third Admission to the Hospital—On March 8, 1937, the patient reentered the hospital. At this time slightly enlarged lymph nodes were noted in the inguinal and in the anterior and posterior cervical regions. The heart was still greatly enlarged. The liver and spleen extended about 2 inches (5 cm) below the costal margin. There was slightly more brownish pigmentation of the skin.

A blood count showed red blood cells, 1,180,000, hemoglobin, 25 per cent, and white blood cells, 22,000. After one blood transfusion the blood count showed red blood cells, 3,070,000, hemoglobin, 30 per cent, white blood cells, 10,900, reticulocytes, 3.2 per cent, normoblasts, 2 per cent, polymorphonuclears, 43 per cent, lymphocytes, 40 per cent, monocytes, 7 per cent, eosinophils, 2 per cent, myelocytes, 4 per cent, metamyelocytes, 3 per cent, and basophils, 1 per cent. There were 116,000 platelets. A fragility test showed beginning hemolysis with 0.325 per cent solution of sodium chloride and complete hemolysis with 0.25 per cent solution. Marked variation in the size, shape and staining of the red blood cells was again noted. Macrocytes, many microcytes and basochromic and stippled cells were

present The van den Bergh test showed 1 unit of bilirubin, and urobilinogen on three occasions was noted as less than 1 to 10 dilution

Clinical Course—During the summer the pigmentation of the skin became extreme, partly because of exposure to the sun The child appeared to grow normally (height and weight), but the temperature showed a daily elevation to about 101 F Various therapeutic agents were employed in an attempt to control the anemia Liver extract and various preparations of iron alone and combined with copper or with liver extract were tried without much success A definite though submaximal reticulocyte response followed parenteral administration of liver extract, reaching a maximum of 8.4 per cent from an initial level of 5.9 per cent



Fig. 3—A roentgenogram of the skull made on July 14, 1936 The outer table appears fairly clear-cut

However, in spite of this and repeated transfusions, the degree of anemia increased On October 4 the red blood cell count was 1,150,000 and the hemoglobin value 17 per cent The leukocyte count varied from 9,000 to 13,000, the reticulocytes from 6 to 9 per cent and the normoblasts from 1 to 10 per cent The van den Bergh test again showed 1 unit of bilirubin and urobilinogen was always noted in a dilution of less than 1 to 10 No increase in the size of the liver or spleen over that noted on entry had occurred

Roentgenograms of the skull and long bones, taken at various intervals, showed progressive enlargement of the marrow cavity and thinning of the cortex but ray formation was not seen in the skull One other negative feature deserves recognition The changes in the bones of the face were never sufficiently marked to

produce the appearance of so-called mongolism, although bulging of the frontal and parietal bones occurred during the third period of hospitalization. This was evident in the last roentgenogram of the skull.

Gonorrheal vulvovaginitis complicated the clinical picture at this time.

Death occurred on Oct 8, 1937.

Postmortem Examination—The body was normally developed. No enlarged lymph nodes were noted. The heart weighed 120 Gm and showed a pale, flabby musculature but no endocardial lesions. The lungs were not remarkable. The thymus weighed 19 Gm. The liver weighed 663 Gm and showed normal markings.



Fig 4—A roentgenogram of the skull made on Aug 12, 1937. The outer table of the skull is ill defined and fuzzy. There is an increase in the marrow cavity.

The spleen weighed 162 Gm. The markings were normal, but the pulp was somewhat more cellular than usual. The kidneys were normal. The pelvic organs showed acute gonorrheal salpingo-oophoritis. The ribs, sternum, femurs, tibiae, vertebral column and frontal and parietal bones were examined. The cortex of all the bones was thin, and the marrow was abundant, dark red and cellular. The most marked thickening was noted in the frontal and parietal bones. The epiphyses of the bones and the costochondral junctions were normal. Histologically the changes in the bone marrow were comparable in every way with those observed at biopsy. The foci of immature undifferentiated cells were large and numerous. Normal myeloid activity occurred about these. Few maturing erythrocytes were

noted Sections of the skin, kidneys, spleen and lymph nodes showed a negative prussian blue reaction Hemosiderosis was marked in the liver, moderate in the pancreas and faint in the bone marrow The pigment of the skin was melanin No foam cells were present in any of the organs

Comment—In summary, the features of the case were (1) the Greek parentage, familial history and onset during the first year of life, (2) the poor development, enlargement of the liver, spleen and heart, pigmentation of the skin, and hypochromic anemia with leuko-



Fig 5—*A* is a roentgenogram of the lower end of the femur of a normal child aged 11 months *B* is a roentgenogram of the lower end of the femur of the patient at the age of 13 months In *B* note the widening of the shaft of the bones and the coarse trabeculation

cytosis, (3) lack of evidence of rickets, syphilis, sickling of the erythrocytes or hemolytic jaundice, (4) a more or less chronic but progressively downhill course that was not materially influenced by known therapeutic measures, and (5) marked hyperplasia of the bone marrow resulting from proliferation but not differentiation of a primitive marrow cell The details of the numerous hemograms are summarized in the accompanying table

Summary of Data

Date	Red Blood Cells, Millions per Cu Mm	Hemoglobin, %	White Blood Cells per Cu Mm	Polymorphon uclears, %	Lymphocytes, %	Monocytes, %	Myelocytes, %	Eosinophils, %	Basophils, %	Metamyelocytes, %	Normoblasts, %	van den Bergh Test, Units	Urobilinogen in Urine	Platelets, Thou sands per Cu Mm	Reticulocytes, %	Weight, Pounds	Enlargement of Liver	Enlargement of Spleen	Temperature, F	Comment
7/13/36	8.1	15	21,400	32	47	10	2		1		6	2.0		208	4.5	17	0	2 1/2	99-101	Fragility test 0.45 to 0.25%, bones thin cortex and expanded medulla
8/ 3/36	2.45	47					2	2	1					115	2.5					
8/31/36	2.25	30	14,300	45	41	9		1	1		7									Gastric analysis free hydrochloric acid Microcytes
9/18/36	2.54	40	8,600	57	39	2		1												Long bones and skull characteristic roent
10/16/36		16	17,000	53	32	5	3	5	2		5	2.0	None		9.9	18				
11/11/36																				
1/19/37	2.05	32	9,150	51	34	11		4			4			188	2.9	19			99	Tragility test 0.375 to 0.25%, marked cardiac enlargement
3/10/37	3.07	30	10,900	43	40	7	4	2	1	1	2			116	3.2	1	+	+++	100	First transfusion, 200 cc
3/19/37	2.11	32	7,000	31	53	10	2	4			3									
3/25/37	1.95	28	8,100	43	40	10	4	2	1					115	2.2	20				
3/31/37	2.02	28	10,700	39	41	15	3	1	0	1	4				4.4	21			101	Second transfusion, 150 cc
4/ 6/37	2.81	36	8,200	51	34	12	1	1	1	5	0			253	1.4	22			100	Third transfusion, 200 cc
4/13/37	3.25	52	9,300	51	31	6	1	6		(degen erite)					0.8					
4/23/37	3.14	57	9,900	51	32	9	1	3			1				1.7					
4/29/37	2.66	48	10,100	57	28	8	1	1		3	0				1.9					
5/ 7/37	3.13	52	7,000	49	37	8	1	1	1		0				0.8	23			101	Fourth transfusion, 240 cc
5/14/37	3.20	56	7,700	34	55	5		1		1	2				0.9					
5/21/37	2.95	59	8,100	40	47	6		2	1	4	4				1.6					
5/28/37	3.06	48	8,200	57	25	7		3	1	4	4				3.5					
6/ 4/37	2.70	44	8,600	44	35	7	1	1		3	10				3.2					
6/11/37	2.56	38	8,200	59	32	3	1	2		3	11				5.3					
6/19/37	2.57	33	10,050	42	44	9	1	2		2	6				5.9	25				June 17 to 21, liver extract
6/25/37	2.30	30	10,000	57	26	8	6	1		1	1				8.3					
7/ 2/37	1.80	26	9,000	66	22	8	1	3		1	10				8.4		+	++		
7/ 9/37	1.17	28	10,700	70	19	3	1	2	1	3	4				5.7	25			101	Fifth transfusion, 200 cc
7/16/37	2.57	48	8,900	55	37	1		1		2	3				4.0					
8/12/37	1.76	28	12,700	34	51	7	1	3	1	3	7	1.0	Less 1/10		8.9					
9/ 3/37												1.0	Less 1/10			25			102	Sixth transfusion, 190 cc, roentgenogram of bones
10/ 4/37	1.15	17																		Seventh transfusion, 255 cc
10/ 6/37	2.20	33																		Death

HISTORICAL RESUME

The historical background of thalassanemia, or Mediterranean disease, may be outlined briefly. In 1889 von Jaksch¹ drew attention to a group of cases of anemia in infancy or early childhood characterized by great enlargement of the spleen, some hepatic swelling, considerable leukocytosis and marked changes in the size and shape of the red blood cells, with varying degrees of chlorotic anemia. In a majority of the cases recovery was spontaneous. The subsequent recognition of this syndrome in cases of congenital syphilis, rickets and other dietary deficiency states served to undermine the decision that von Jaksch's disease is a clinical entity. The condition came to be recognized as a biologic variant of ordinary secondary anemia or, to quote Naegeli,² "not a special entity but an extreme reaction."

Thomas B. Cooley,³ of Detroit, deserves the credit for saving the entity from utter dissolution. In 1925 he pointed out that certain patients with von Jaksch's disease reacted peculiarly after splenectomy, in that the blood showed postoperatively great numbers of nucleated red cells. He further showed that these patients exhibited other common characteristics: 1. The disease was usually confined to infants of Syrian, Greek or Italian parentage. 2. The children had a sallow complexion—subicteric but not definitely jaundiced. 3. They often presented the appearance of mongolism, partly because of the color of the skin and partly because of prominence of the bones of the cheek as a result of hyperplasia of the marrow. 4. They were undersized, and the abdomen was prominent, owing to splenic and hepatic enlargement. 5. Adenopathy was sometimes present. 6. Secondary phenomena of anemia—cardiac dilatation and murmurs, and serous effusions—were proportionate to the stage and severity of the disease. 7. As regards the blood, pigmentation of the serum was common but was not always present. The anemia was of the hypochromic type, with marked variation in the size and shape of the red blood cells. Basochromic stippling and nucleated forms were numerous. The proportion of reticulocytes sometimes reached that which is typical of hemolytic jaundice. The grade of

1 von Jaksch, R. Ueber Leukämie und Leukocytose im Kindesalter, *Wien klin Wchnschr* 2:435, 1889.

2 Naegeli. Allgemeine Gesichtspunkte über Anämien, deren Entstehung und Einteilung, *Schweiz med Wchnschr* 55:1043, 1925.

3 Cooley, T. B., and Lee, P. A Series of Cases of Splenomegaly in Children, with Anemia and Peculiar Bone Changes, *Tr Am Pediat Soc* 37:29, 1925.
Cooley, T. B. Von Jaksch's Anemia, *Am J Dis Child* 33:786 (May) 1927.
Cooley, T. B., Witwer, E. R., and Lee, P. Anemia in Children with Splenomegaly and Peculiar Changes in the Bones. Report of Cases *ibid* 34:347 (Sept) 1927.
Cooley, T. B. Likenesses and Contrasts in the Hemolytic Anemias of Childhood, *ibid* 36:1257 (Dec) 1928.

anemia was moderate except during exacerbations due to malnutrition or intercurrent infection or in the terminal stage 8 The white blood cell count was always increased, the average being almost 20,000 Lymphocytes predominated, but marrow cells were often present, sometimes in considerable number The platelets were not affected The fragility of the red blood cells was normal, and sickling did not occur In the urine, urobilinogen was at times present in excess, but this was not constant 9 The spleen was greatly enlarged, the capsule was thick and at times there was perisplenitis The follicles were small and scarce, being crowded out by the pulp cells, which consisted partly of areas of erythropoietic and myeloid activity Both liver and spleen showed, in varying degrees, an increase in the amount of connective tissue 10 The bone marrow was hyperplastic, and the cortex of the bone was thin and was encroached on by the marrow This was especially marked in the skull, which was often several times the normal thickness In the earlier stages the elements forming both red and white cells were increased, but later erythropoiesis failed, through exhaustion Trabeculae of new bone then appeared This gave rise to a raylike appearance in the roentgenograms 11 The clinical course of the disease was usually chronic but inevitably fatal before puberty In some cases progress was rapid Splenectomy was without permanent benefit Cooley said he believed that the disease has points of resemblance to hemolytic icterus and sickle cell anemia (splenomegaly, anemia, reticulocytosis, hyperplastic marrow and familial tendency) and to pernicious anemia

Since Cooley's outstanding contribution, little has been added, either to the clinical picture or to the pathologic features, although many cases have been reported and the syndrome is generally recognized as a disease entity In 1936 Whipple and Bradford,⁴ of Rochester, N Y, reported 8 cases and coined a new name for the disease—thalassanemia, or Mediterranean disease, because of its predilection for children of Syrian, Greek, Italian or Armenian parents These authors, who studied in detail the pathologic material from 5 patients, stated that the disturbance in pigment metabolism is comparable to that in hemochromatosis They reported the frequent occurrence of foci of foam cells in the spleen, liver, lymph nodes and bone marrow similar to those found in cases of Gaucher's disease They said they had tried unsuccessfully the therapeutic effect of blood transfusions, plasma and cell extracts, "primary or secondary anemia liver extracts," fetal liver extract, spleen extract, raw pancreas, adrenal cortex extract (cortin), estrogenic substance, vitamin B₁ concentrate, iron, and copper They

4 Whipple, G H, and Bradford, W L Mediterranean Disease—Thalassemia (Erythroblastic Anemia of Cooley) Associated Pigment Abnormalities Simulating Hemochromatosis, *J Pediat* 9 279, 1936

concluded that the disease is due to some inherited racial defect which is responsible for the abnormalities of the hemopoietic tissues (of the order of pernicious anemia), the osseous changes (of the order of acromegaly) and the abnormalities of the pigment (identical with those in hemochromatosis). They further suggested that the deficiency state may be remediable when better understood.

COMMENT

The case just reported differs in some details from the classic features described by Whipple and Bradford. The bones never showed the marked changes necessary to produce the typical facies of mongolism or "raying" in the roentgenograms although pathologically they were characteristic except for the absence of foam cells. Hemosiderosis was noted only in the liver and pancreas, although sections of skin and parenchymatous organs were stained with this in mind. Finally, the degree of erythroblastosis and leukocytosis commonly reported was never noted, although twenty-five complete hemograms were made over a period of eighteen months. The maximum number of normoblasts found was 11 per hundred leukocytes, and the reticulocyte count never exceeded 9.9 per cent. The color index was commonly at or below unity. Macrocytes and microcytes occurred in all smears, but the latter predominated. Leukocytosis was not a feature of the disease. In fact, only four of twenty-five determinations showed the white blood cell count to be above the accepted normal standards for a child of this age. The differential leukocyte count was likewise within normal limits. The abnormal features in the hemogram were, therefore, normoblastosis and reticulocytosis, with severe anemia of the orthochromic type. The results of fractional gastric analysis indicated that gastric acidity was within normal limits. Neither the clinical nor the pathologic features of this case support the suggestion that this disease is comparable to pernicious anemia or hemochromatosis.

In conclusion, the minimal requirements for the diagnosis of thalassanemia seem to be (1) pigmentation of the skin, whether from deposition of melanin or of hemosiderin, (2) an increase in the marrow cavity of the bones, detectable clinically or roentgenographically, (3) enlargement of the spleen, (4) intractable anemia, with some degree of reticulocytosis and erythroblastosis, and (5) hemosiderosis of the liver and pancreas.

SUMMARY AND CONCLUSIONS

A case of thalassanemia in a child of Greek parentage is reported. Two of her brothers had died as the result of a similar condition. Roentgenograms of the skull did not show "raying," and foam cells were not present in the bone marrow or spleen. Pigmentation of the skin

was due to deposition of melanin, not hemosiderin. Hemosiderosis was present only in the liver and pancreas. Pseudoleukemia did not occur. The gastric contents contained free hydrochloric acid.

Thalassanemia seems to be due primarily to failure of certain primitive marrow cells to undergo normal maturation.

Prof. H. B. Cushing gave me permission to publish a report of this case, and Dr. A. E. Childe supplied the photographs.

SYMPATHETIC VASODILATOR FIBERS IN THE UPPER AND LOWER EXTREMITIES

OBSERVATIONS CONCERNING THE MECHANISM OF INDIRECT VASODILATATION INDUCED BY HEAT

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In 1890 Sewall and Sanford ¹ found that placing one upper extremity in warm water induced vasodilatation in the fingers of the opposite hand. They estimated the blood flow to the digits by means of a plethysmograph. In 1911 Stewart ² corroborated this observation by means of calorimetric determinations of the blood flow to the hand. More recently this phenomenon of indirect vasodilatation induced by heat has been studied carefully by several investigators,³ and a great deal has been learned concerning the mechanism of its production. Pickering^{3c} first showed that in human beings vasodilatation induced in one extremity by warming another depends on the return of the blood from the

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The terms indirect vasodilatation induced by heat and indirect vasodilatation are used in this paper to indicate vasodilatation in the extremities as a result of warming another part of the body either by immersing in warm water another extremity or two extremities or by exposing the trunk to radiant heat

1 Sewall, H, and Sanford, E. Plethysmographic Studies of the Human Vaso-Motor Mechanism When Excited by Electrical Stimulation, *J Physiol* **11** 179-207, 1890

2 Stewart, G N. Studies on the Circulation in Man. II The Effect of Reflex Vaso-Motor Excitation on the Blood Flow in the Hand, *Heart* **3** 76-88, 1911

3 (a) Lewis, T, and Pickering, G W. Vasodilation in the Limbs in Response to Warming the Body, with Evidence for Sympathetic Vasodilator Nerves in Man, *Heart* **16** 33-51 (Oct) 1931. (b) Gibbon, J H, Jr, and Landis, E M. Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, *J Clin Investigation* **11** 1019-1036 (Sept) 1932. (c) Pickering, G W, and Hess, W. Vasodilatation in the Hands and Feet in Response to Warming the Body, *Clin Sc* **1** 213-223 (Dec) 1933. (d) Uprus, V, Gaylor, J B, and Carmichael, E A. Vasodilatation and Vasoconstriction in Response to Warming and Cooling the Body. A Criticism of Methods, *ibid* **2** 301-316 (Dec) 1936. (e) Pickering, G W. The Vasomotor Regulation of Heat Loss from the Human Skin in Relation to External Temperature, *Heart* **16** 115-135 (Jul) 1932

warmed extremity to the general circulation. He estimated the blood flow to the hand calorimetrically. Gibbon and Landis^{3b} later showed that intermittent occlusion of the arterial and venous circulation of the extremity immersed in warm water prevents vasodilatation in the unimmersed upper extremities for a period at least as long as intermittent occlusion is maintained. They showed, further, that indirect vasodilatation occurs in the upper extremity even if the lower extremity which is immersed in warm water is decentralized completely as far as its somatic and sympathetic nerve supply is concerned. These experiments, of course, corroborated the findings of Pickering. The available evidence⁴ indicates that the change in the blood which occurs as a result of its passage through the warmed extremity and which induces vasodilatation in the remaining extremities is an increase in temperature. It has been pointed out^{3d} also that the important factor with regard to the change in the temperature of the blood so far as it concerns indirect vasodilatation produced by immersion of an extremity in warm water is the gradient or steepness of the rise rather than the actual temperature of the blood itself. It should be noted, however, that the possibility never has been disproved that some product of metabolism capable of producing vasodilatation through its central action is added to the blood as it passes through the warmed extremity.

Lewis and Pickering^{3a} were the first to show that in human beings the occurrence of indirect vasodilatation in the digits of an upper extremity depends on the integrity of the sympathetic nerves supplying these digits. This observation has been corroborated amply.⁵ It must be assumed, therefore, that indirect vasodilatation induced in one extremity by warming another extremity is due to either the stimulating or the inhibiting action of the blood, which is returning from the warmed extremity at an increased temperature, on some center capable of increasing the blood flow to the extremities. The actual vasodilatation in the extremity then occurs as a result of nervous influences which are mediated by the sympathetic nerves and which result in relaxation of the smooth muscle of the vessels and a consequent increase in blood flow to the extremity.

It appears, on theoretic grounds, that changes induced in the vasomotor center by an increase in the temperature of the blood might result in vasodilatation in the extremities either by giving rise to

4 Uprus, Gaylor and Carmichael^{3d} Pickering^{3e}

5 (a) Freeman, N. E. The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am J Physiol* **113** 384-398 (Oct.) 1935. (b) Prinzmetal, M., and Wilson, C. The Nature of the Peripheral Resistance in Arterial Hypertension, with Special Reference to the Vasomotor System, *J Clin Investigation* **15** 63-83 (Jan.) 1936. Gibbon and Landis^{3b}

vasodilator nerve impulses, which presumably would travel over vasodilator nerve fibers, or by inhibiting vasoconstrictor impulses. It is probable that, under ordinary circumstances reflex vasodilatation in the digits occurs primarily as the result of inhibition of vasoconstrictor impulses rather than as the result of active vasodilator impulses.^{2a}

It remains of importance to know, however, aside from any practical usefulness which they might have, whether or not vasodilator fibers are present in the sympathetic nerves supplying the extremities in man. Lewis and Pickering^{3a} brought forth evidence which indicated that vasodilator fibers are present in the sympathetic nerves supplying the upper extremities of patients with Raynaud's disease and that these fibers are an important part of the mechanism which mediates indirect vasodilatation in cool environmental temperatures. They showed in certain patients with Raynaud's disease, in whom exposure to cold easily produced and maintained digital arterial spasm, that block of the ulnar nerve usually was not sufficient to produce vasodilatation in the fifth finger if the environmental temperature was sufficiently cool (14 to 16 C). Furthermore, this procedure prevented for a time the occurrence of reflex vasodilatation in the anesthetized fifth finger. This failure of vasodilatation to occur in the anesthetized finger while it was occurring in the unanesthetized fingers led these investigators to the conclusion that sympathetic vasodilator fibers are present in the ulnar nerve. This conclusion was based on the assumption that indirect vasodilatation did not occur in the anesthetized finger because the sympathetic vasodilator fibers were blocked, whereas it did occur in the unanesthetized fingers, by virtue of the intact sympathetic vasodilator fibers.

This work, to our knowledge, never has been corroborated. Furthermore, Lewis and Pickering did not report any observations relative to the presence or absence of vasodilator fibers in the lower extremities. It is our object in this communication, therefore, to report experiments relative to the presence of sympathetic vasodilator fibers in both the upper and the lower extremities and other observations concerning the mechanism of indirect vasodilatation induced by heat.

METHOD OF INVESTIGATION

The observations here reported concern vasodilatation in the digits of the upper and lower extremities. The blood flow was measured by means of determinations of the temperature of the skin, which were made with an electromotive thermometer of the type described by Sheard.⁶ A decrease in the temperature of the skin was assumed to represent a decrease in blood flow, whereas an increase in the temperature was assumed to represent an increase in blood flow. The determinations of the temperature of the skin were made on the volar or

⁶ Sheard, C. The Electromotive Thermometer. An Instrument and a Method for Measuring Intramural, Intravenous, Superficial and Cavity Temperatures, *Am J Clin Path* 1: 209-226 (May) 1931.

plantar surfaces of the distal phalanges of the fingers and toes, respectively. The rectal temperature was determined by means of the same instrument, the copper-constantan junction being inserted into the rectum well above the internal anal sphincter. The observations were carried out with the room temperature and humidity accurately controlled. The temperature of the room was determined by means of a thermocouple suspended in the air in the vicinity of the digits being investigated. During the course of the experiments the subject reclined on a comfortable couch. Indirect vasodilatation was induced either by immersing a lower extremity in warm water to a point just below the knee or an upper extremity to a point just above the elbow or by the use of a radiant heat tent over the trunk, a sufficient number of blankets being thrown over the tent to maintain the heat in the vicinity of the trunk and to prevent it from materially influencing the temperature of the room. The water was maintained at a fairly constant temperature by means of an especially constructed can into which a thermostat was built. The temperature of the heat tent was regulated by the number of bulbs which were allowed to burn. Obstruction of the venous circulation in the extremities was carried out by means of an ordinary mercury sphygmomanometer, the cuff being placed proximal to the line of immersion. Nerve block and regional anesthesia were obtained by the use of a 2 per cent solution of procaine hydrochloride without epinephrine.

EXPERIMENTAL RESULTS

Figure 1 portrays a characteristic vasodilator response in the finger and toe of a normal person. This response resulted from immersion of a lower extremity in warm water. Vasodilatation occurred first in the finger and later in the toe. This delayed response in the toes had been observed previously⁷ and had been attributed by Pickering and Hess to a difference in the intensity of the vasomotor relaxation in the upper and in the lower extremities. That vasomotor relaxation can be produced with greater ease in the upper than in the lower extremities is an established fact. Horton, Roth and Adson⁸ showed conclusively that vasodilatation occurs more consistently and to a greater degree in the fingers than in the toes after the intravenous injection of typhoid vaccine, whereas Crisler and one of us (D. Allen⁹) demonstrated that this same relation holds when acetylbetamethylcholine (mecholyl) is injected either intravenously or intra-arterially. To be sure, the vasodilatation is greater in the fingers than in the toes, even when the drug is injected into the femoral artery. We have not observed failure of indirect vasodilatation to occur in either the upper or the lower extremities of normal persons as a result of immersing one extremity in warm water (42 to 44 C), the environmental temperatures being 16

7 Gibbon and Landis^{2b} Pickering and Hess^{3c}

8 Horton, B. T., Roth, G. M., and Adson, A. W. Observations on Some Differences in the Vasomotor Reactions of the Hands and Feet, *Proc. Staff Meet. Mayo Clin.* **11** 433-437 (July 8) 1936.

9 Allen, E. V., and Crisler, G. R. The Result of Intra-Arterial Injection of Vasodilating Drugs on the Circulation. Observations of Vasomotor Gradient. *J. Clin. Investigation* **16** 649-652 (July) 1937.

to 27 C. We studied a patient who had Raynaud's disease involving the lower extremities. Simultaneous immersion of both an upper and a lower extremity in water at 42 to 44 C and the presence of an environmental temperature greater than 50 C about the trunk failed to produce indirect vasodilatation in the lower extremity when the environmental temperature was 27 C. An environmental temperature of 50 to 60 C about the trunk invariably produced vasodilatation in the upper extremities of normal persons but not infrequently failed to do so in the lower extremities. Pickering and Hess^{3c} cited the instance of a normal person whom they observed warming his body by immersion of an

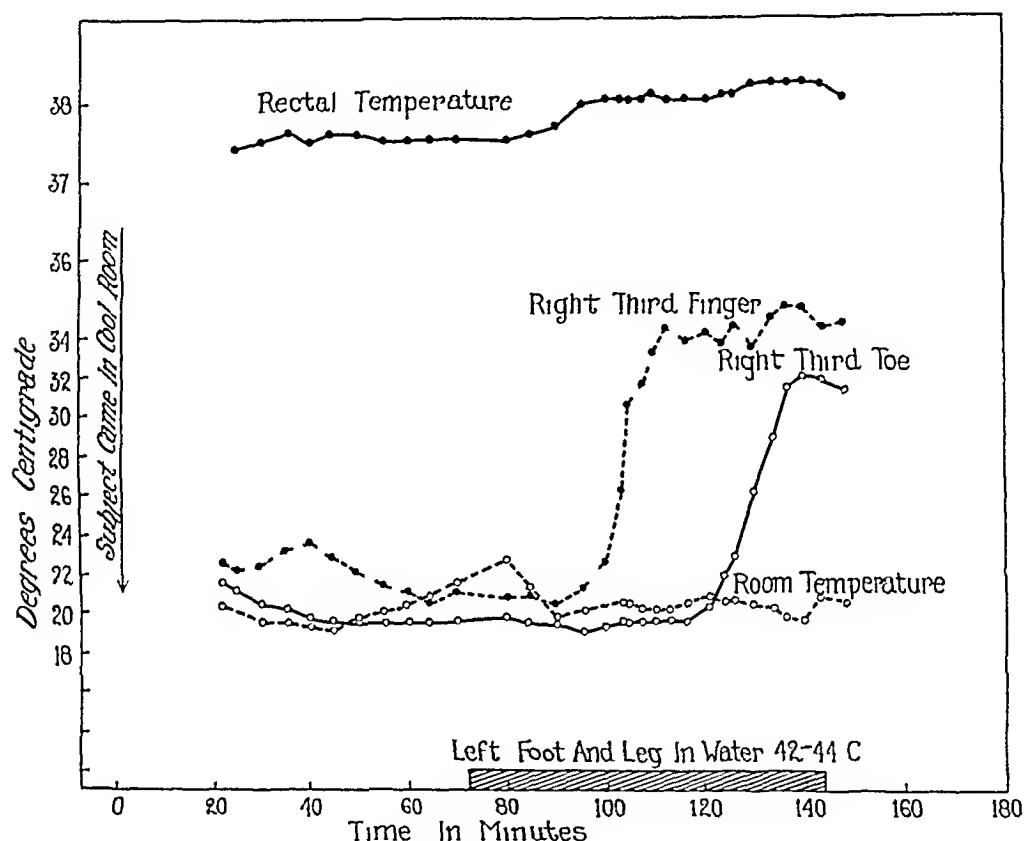


Fig 1—A characteristic response of the temperature of the skin of a finger and of a toe to immersion of a leg in warm water. Vasodilatation did not begin until after a rise in rectal temperature had occurred. Vasodilatation occurred more quickly and apparently was greater in the finger than in the toe.

upper and a lower extremity in water at 42 to 44 C failed to produce vasodilatation in the toes when the foot had been cooled thoroughly. Thus, it appears that warming the body by immersion of one or two extremities in warm water cannot always be depended on to produce indirect vasodilatation in the toes of persons who do not have organic occlusive arterial disease. Conversely, failure of vasodilatation to occur in the feet as a result of this procedure does not necessarily mean that the blood supply to the feet is impaired by organic arterial occlusion.

This method appears to be reliable for the determination of the adequacy of the arterial supply to the hand

Indirect vasodilatation as a result of warming the body by placing an extremity in warm water is dependent on the return of the blood circulating through the warmed extremity to the general circulation. The experiments of Pickering^{3a} and of Gibbon and Landis^{3b} proved that this is true for indirect vasodilatation in the upper extremity, as mentioned previously. In their experiments they prevented the return of the blood from the warmed extremity to the general circulation by means of a cuff which occluded both the arterial and the venous circulation.

It occurred to us that the dependency of indirect vasodilatation on the return of the blood from the warmed extremity to the general circulation could be demonstrated more simply by occluding the venous circulation of the immersed extremity proximal to the line of immersion without occluding the arterial inflow. This we accomplished by placing an ordinary cuff of a sphygmomanometer around the extremity and then elevating and maintaining the pressure within the cuff at a level corresponding to 50 to 60 mm. of mercury. It is probable, of course, that this procedure does not produce complete venous occlusion for a long period. Nonetheless, it undoubtedly reduces the venous return from the part of the extremity distal to the cuff to a small fraction of what it would be normally. Furthermore, it was adequate for the purpose of illustrating the point in question, as may be seen in figure 2. Here, impairment of the return of the venous blood to the general circulation from the warmed extremity by means of the inflated cuff prevented appreciable indirect vasodilatation as long as the cuff was inflated. We repeated this experiment on 2 normal persons, with the same result. These experiments show, therefore, that indirect vasodilatation induced in the toes by means of warming the body by immersing an extremity in warm water depends on the return of the venous blood from the warmed extremity to the general circulation.

Similarly, indirect vasodilatation in the fingers can be demonstrated by the same method to depend on the same factor, provided the environmental temperature is sufficiently low to keep the fingers relatively cool while the cuff is inflated. In two experiments we demonstrated by the method described that impairment of the venous return of the warmed extremity delayed indirect vasodilatation in the fingers until the cuff was released.

In summary, then, we may say that indirect vasodilatation in the toes and fingers induced by warming another extremity depends on the return of the venous blood from the warmed extremity to the general circulation.

Indirect vasodilatation induced by heat depends on the integrity of the sympathetic nerves supplying the part in which vasodilatation is produced. This point is illustrated in figure 3. We have observed that either placing an extremity in warm water or increasing the environmental temperature about the trunk will not produce an appreciable increase in the temperature of the skin of the digits indirectly if the sympathetic nerves to the digits are not intact. These experiments corroborate previous observations relative to this point¹⁰

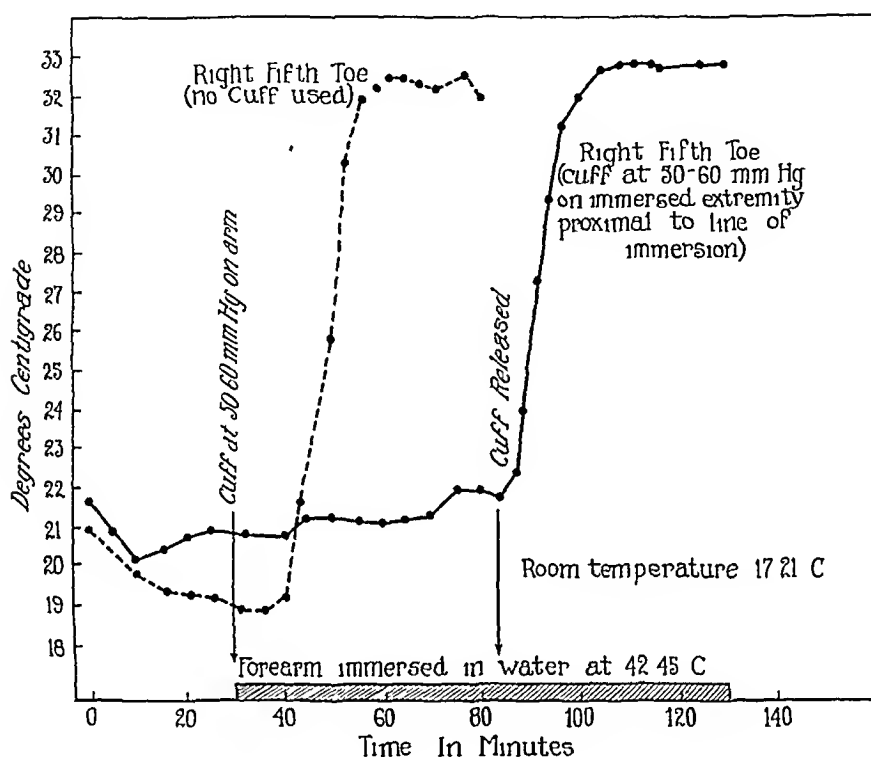


Fig 2—Two experiments were performed on a normal subject at different times. The experiments were carried out in identically the same way as the experiment shown in figure 1 with regard to the time relation. When the venous circulation of the warmed forearm was not occluded, vasodilatation in the toe began within fourteen minutes after immersion of the forearm in warm water. However, when the cuff was placed on the immersed extremity proximal to the line of immersion, appreciable vasodilatation did not occur until the cuff (which prevented the flow of venous blood) was removed. When the cuff was not used, the room temperature varied from 17 to 17.8°C. When the cuff was used the room temperature varied from 19.8 to 21.3°C.

Since indirect vasodilatation in a digit depends on the integrity of the sympathetic nerves supplying the digital vessels, it is obvious that the stimulus which gives rise to the vasodilatation acts at some central site, presumably the vasomotor center, and that the effect of this central

¹⁰ Lewis and Pickering^{3a} Gibbon and Landis^{3b} Freeman^{5a} Prinzmetal and Wilson^{5b}

stimulus is transmitted to the peripherally situated digital vessels by means of the sympathetic nerves. On theoretic grounds, a central stimulus could produce peripheral vasodilatation either by inhibiting the outflow of vasoconstrictor impulses from the vasomotor center or by giving rise to active vasodilator impulses. Under ordinary circumstances it is possible that inhibition of vasoconstrictor impulses is chiefly responsible for reflex vasodilatation. This is true because of the fact that blockage of the sympathetic nerves to a digit usually results in vasodilatation, owing to cessation of central vasoconstrictor influences. However, under certain conditions it appears that blockage of the vasoconstrictor impulses is not sufficient to result in vasodilatation.

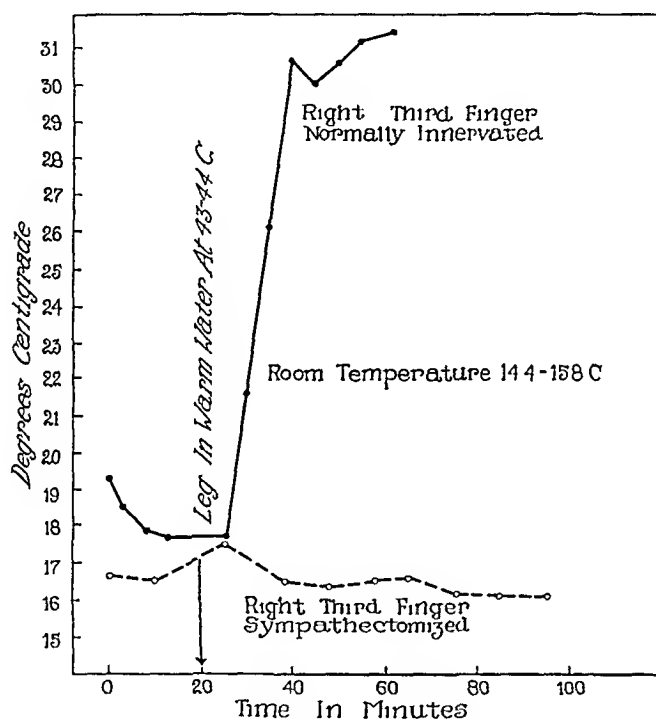


Fig 3—Experiments were performed on 2 patients with Raynaud's disease. One patient had a normally innervated finger, and the other had previously undergone sympathectomy of the preganglionic type. It is apparent that reflex vasodilatation occurred readily in the normally innervated digit, whereas it failed to occur within a period of seventy-four minutes in the sympathectomized digit.

Lewis and Pickering³¹ have shown that this is true for the fingers of patients with Raynaud's disease in sufficiently cool environmental temperatures, and their evidence indicates that reflex vasodilatation in these cases is brought about by means of active vasodilator impulses transmitted along sympathetic vasodilator nerves. The observations to be recorded here corroborate the evidence presented by Lewis and Pickering favoring the view that there are sympathetic vasodilator fibers in

the upper extremities of man, and they indicate that there are also sympathetic vasodilator fibers in the lower extremities

The inhibitive effect of blockage of the ulnar nerve, performed in a cool environmental temperature, on reflex vasodilatation in the anesthetized fifth finger is shown in figure 4. The patient was a Norwegian farmer aged 47 who for four years had noted hyperhidrosis, vasospastic phenomena on exposure to cold and sclerodermatous changes in both the hands and the feet. All these symptoms were of moderately severe intensity. After the sensory and sympathetic nerve fibers in the left

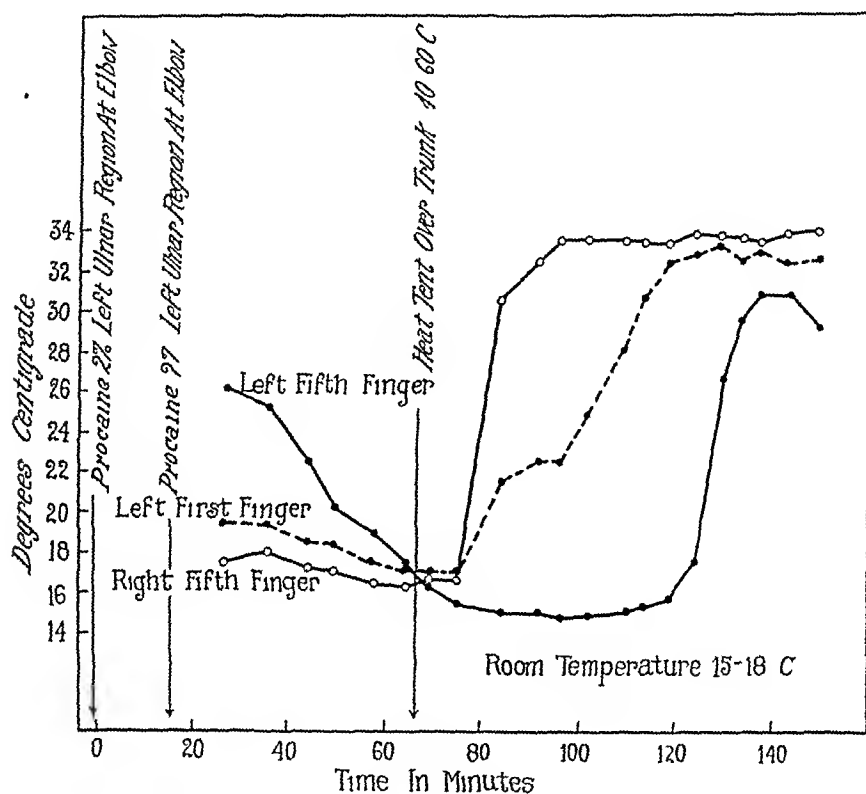


Fig 4—The effect of ulnar nerve block (procaine hydrochloride), performed in a cool environmental temperature, on reflex vasodilatation induced by heat. The patient had moderately severe Raynaud's disease associated with sclerodactylia. In the unanesthetized left first and right fifth fingers, vasodilatation (as indicated by a rise in skin temperature) began nine minutes after the heat tent was placed over the trunk. In the anesthetized left fifth finger, appreciable vasodilatation did not occur until fifty-eight minutes after the heat tent was placed over the trunk, when anesthesia was diminishing.

fifth finger had been blocked temporarily by anesthetization of the ulnar nerve at the elbow,¹¹ vasodilatation did not begin in this finger until

11 Lewis, T. Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers. A Variety of Raynaud's Disease, *Heart* 15 7-10 (Aug) 1929.

fifty-eight minutes after the heat tent was placed over the trunk, whereas in the unanesthetized fingers, vasodilatation began nine minutes after the heat tent was placed over the trunk. Thus, vasodilatation in the anesthetized finger was delayed for forty-nine minutes. Ultimate vasodilatation in the anesthetized finger was expected to occur, for the palmar vessels obviously sooner or later would be warmed by the blood returning from the warm, normally innervated fingers. Lewis¹¹ has shown that warming the palm alone will release the spasm of the palmar arch and its digital branches in cases of Raynaud's disease. Another possible explanation for the ultimate vasodilatation in the anesthetized fifth finger is a diminution in the effect of procaine hydrochloride at the time of or previous to vasodilatation. In the instance just cited, the anesthesia was beginning to diminish about the time vasodilatation occurred, although sensation was not normal again until after the experiment had been completed.

As there is, to our knowledge, no reliable evidence to indicate that there are vasodilator sympathetic fibers supplying the lower extremities in man, we utilized the principle of the method that has been described to investigate this problem with respect to the lower extremities.

It is, of course, a well known fact, concerning both the upper and the lower extremities, that peripheral nerve block will result under ordinary circumstances in vasodilatation in the regions supplied by the nerve provided there is no organic vascular occlusion. Regional nerve block ("ring block" at the base of the finger or "bunion block" of the great toe) will produce a similar effect under ordinary environmental conditions, as Simpson, Brown and Adson¹² observed in respect to the upper extremities and as we have observed in respect to the lower extremities. A similar effect occurs in the normal lower extremities in environmental temperatures as low as 15 C. An example of the effect of regional nerve block of the left first toe of a normal person in a fairly cool environment is shown in figure 5. Obviously, in this instance the local effect of cold on the vessels supplying the great toe was not sufficient to overcome the effect of sympathetic nerve block produced by procaine hydrochloride, and vasodilatation occurred in the anesthetized toe. Such vasodilatation most probably is due to obstruction of central vasoconstrictor impulses. It assuredly is not solely due to active central sympathetic vasodilator impulses, because the sympathetic nerve supply to the toe has been interrupted temporarily by the procaine.

However, in the study of the effect of regional nerve block of the toes of patients with moderate or severe symptoms of Raynaud's dis-

12 Simpson, S. L., Brown, G. E., and Adson, A. W. Raynaud's Disease: Evidence That It Is a Type of Vasomotor Neurosis, *Arch. Neurol. & Psychiat.* 26: 687-718 (Oct.) 1931.

ease in the feet in cool environmental temperatures, a different result is obtained. This is illustrated in figures 6 and 7. The first patient (fig 6), a woman aged 19, had experienced moderately severe vasospastic symptoms in both hands and feet on exposure to cold for three months. She also had moderately severe rheumatoid arthritis involving the joints of all four extremities. Regional nerve block in this case, with resultant cessation of the central vasoconstrictor impulses, was not sufficient to produce vasodilatation which would cause an appreciable elevation of the temperature of the skin. In other words, the local effect of the cold environment was sufficient to maintain vasoconstriction in the digital vessels even after the central sympathetic vasoconstrictor impulses were no longer allowed to influence the vessels. The regional

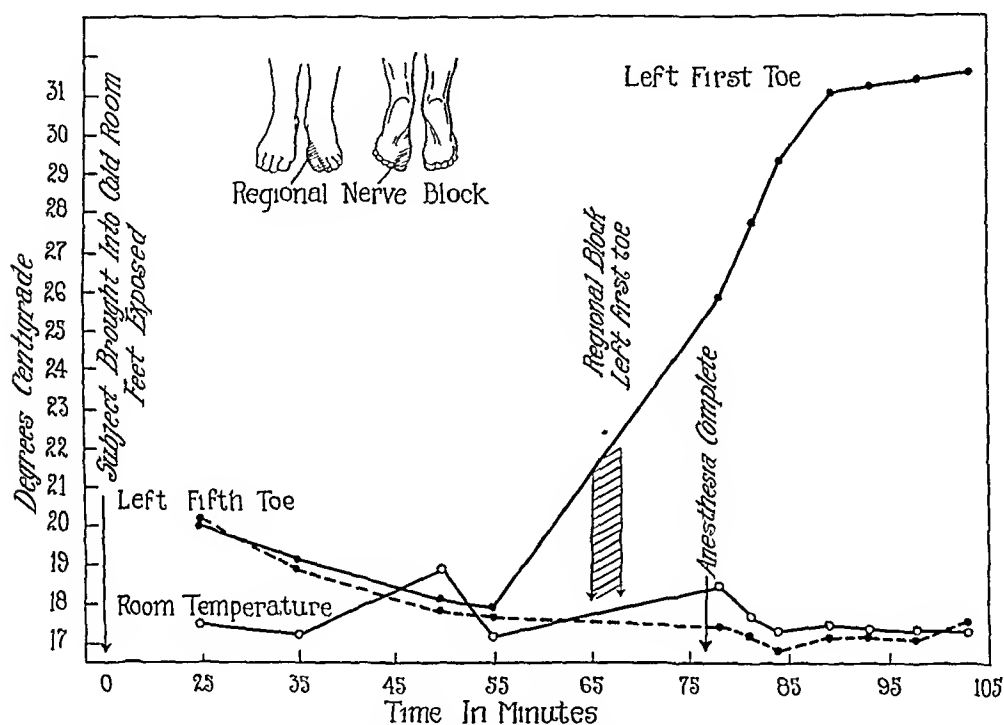


Fig 5—The effect of regional nerve block of the left first toe of a normal person in a fairly cool environmental temperature (17 to 19 C). Marked vasodilatation occurred in the anesthetized toe, whereas the unanesthetized fifth toe remained at room temperature. In this instance removal of the central vasoconstrictor influence was sufficient to result in vasodilatation.

anesthesia not only had blocked the sympathetic vasoconstrictor nerve fibers to the great toe and prevented the passage of central vasoconstrictor impulses along these fibers but also had blocked any sympathetic vasodilator fibers which might have been supplying the vessels of the great toe.

If sympathetic vasodilator fibers, which presumably would transmit central sympathetic vasodilator impulses, are normally present in the sympathetic nerves supplying the toes, it would be expected, when these fibers are blocked by procaine, that central stimulation of these

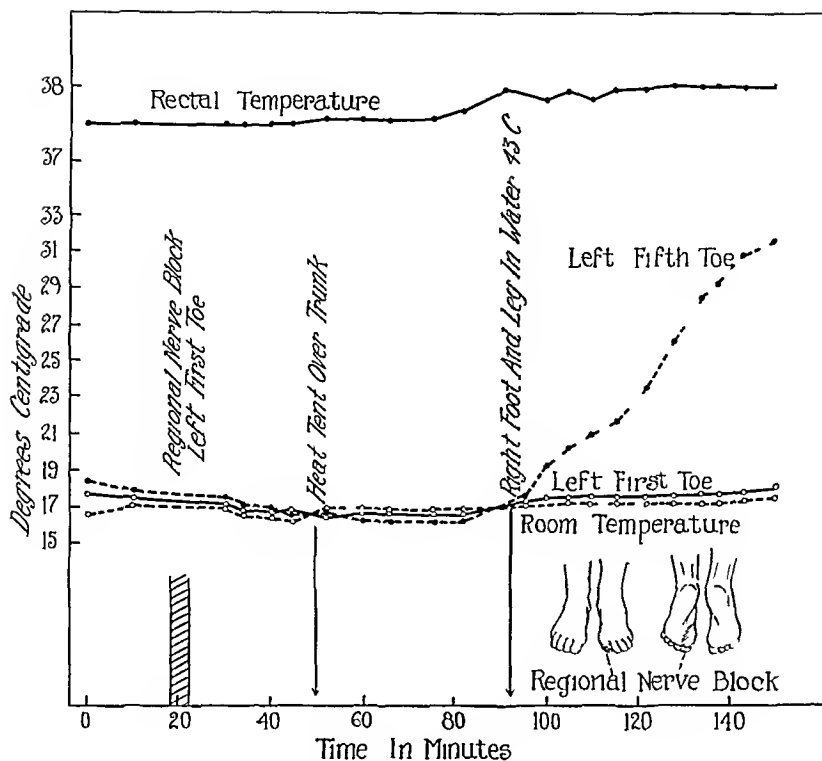


Fig 6—The effect of regional nerve block on reflex vasodilatation induced by heat in a cool environmental temperature in a case of moderately severe Raynaud's disease. The nerve block was not sufficient to overcome the local effect of cold, and vasodilatation failed to occur in the anesthetized toe. Heating the trunk and placing the right foot and leg in warm water produced vasodilatation in the normally innervated fifth toe but failed to do so in the anesthetized toe, presumably because the vasodilator fibers to this toe were blocked.

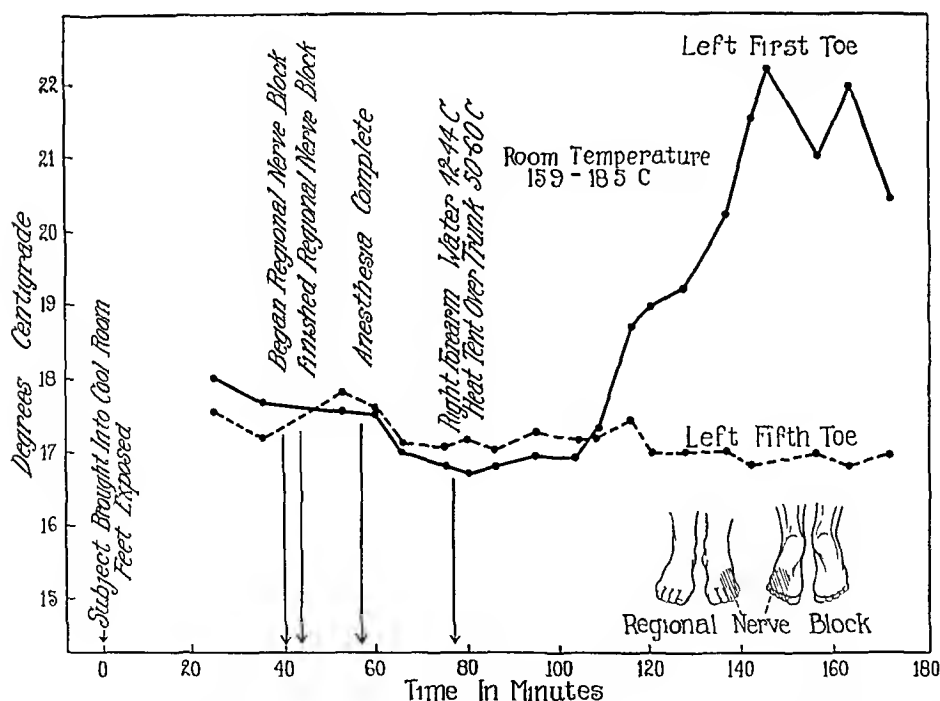


Fig 7—The effect of regional nerve block on reflex vasodilatation induced by heat in a cool environmental temperature in a case of moderately severe Raynaud's disease. The result obtained was essentially the same as that presented in figure 6.

fibers, for example, by an increase in the temperature of the blood, would not result in vasodilatation in the anesthetized toe but in vasodilatation in the unanesthetized toes, the vasodilator fibers of which would be intact. This supposition would be true, of course, only if indirect vasodilatation under the conditions of the experiment depended on the integrity of the sympathetic vasodilator fibers. Figure 6 demonstrates that under the conditions of this experiment, regional nerve block may prevent reflex vasodilatation, and this evidence, on the basis of the aforementioned reasoning, indicates that there are sympathetic vasodilator nerves in the lower extremities.

In the experiment illustrated in figure 6, regional nerve block had failed to result in vasodilatation in the left first toe, so a heat tent was placed over the trunk at the fiftieth minute of the experiment. There was no appreciable change in the rectal temperature until the eighty-second minute. As it was possible that this warm environmental temperature about the trunk would not be sufficient to produce vasodilatation in the toes under the circumstances, the right lower extremity was immersed in water at 43 C to a point just below the knee. As can be seen, marked vasodilatation occurred in the unanesthetized fifth toe, the sympathetic nerves of which were intact, whereas no appreciable vasodilatation occurred in the anesthetized first toe, the sympathetic nerves of which were blocked. A repetition of this experiment two days later under practically the same conditions, with the exception that the regional injection of procaine hydrochloride was omitted, resulted in the expected vasodilatation in the left first toe, thus showing that the stimulus used was sufficient to produce vasodilatation in the left first toe when the sympathetic nerves were intact.

A similar result was obtained in another case of moderately severe Raynaud's disease, as indicated in figure 7. This patient, a housewife aged 50, had been troubled for twenty-two years with vasospastic symptoms in the hands and feet on exposure to cold. She also had mild sclerodermatous changes in the upper and lower extremities and in the face. For eight years she had had calcinosis cutis of the fingers and toes. In this instance, reflex vasodilatation failed to occur in the fifth toe when the sympathetic nerves had been blocked, while it was occurring in the first toe, where the sympathetic nerves were intact.

It appears, therefore, that in the sympathetic nerves supplying the lower extremities of patients with Raynaud's disease, nerve fibers are present which are a necessary part of the mechanism that results in indirect vasodilatation in a cool environmental temperature. Furthermore, regional nerve block is capable of inactivating these fibers, thus preventing reflex vasodilatation in the digits supplied by them. These nerve fibers cannot be vasoconstrictor fibers, because block of vasocon-

strictor nerves prevents the passage of central vasoconstrictor impulses and releases the central vasoconstrictor influence, thus tending to produce rather than prevent vasodilatation. As the integrity of these fibers is necessary for reflex vasodilatation, as is evidenced by the fact that blocking prevents this vasodilatation, it is necessary to conclude that they are vasodilator fibers. These experiments constitute evidence, therefore, in favor of the view that sympathetic vasodilator fibers are present in both the upper and the lower extremities in man.

We have attempted repeatedly to demonstrate the presence of sympathetic vasodilator fibers in the extremities of normal persons by this method, but we have never been successful. For example, we performed ulnar nerve block in an environmental temperature of 0 C, with the idea in mind that perhaps the cooler air surrounding the fifth finger might overcome the vasodilator effect of blocking the central vasoconstrictor impulses. However, we found that ulnar nerve block under these conditions resulted in definite elevation of the temperature of the skin of the fifth finger, thus indicating that, even at a temperature of 0 C, blockage of the sympathetic vasoconstrictor impulses is sufficient to result in vasodilatation. Also, we found that with an environmental temperature of 15 C or more (up to 27 C), regional nerve block of the toes always resulted in vasodilatation in the anesthetized toes of normal persons. Furthermore, we attempted to demonstrate the presence of sympathetic vasodilator fibers by comparing the magnitude of the indirect vasodilator response to heat, as indicated by changes in the temperature of the skin of normally innervated and of acutely denervated digits. However, we were unable to show any consistently greater increase in the temperature of the normally innervated digits. Therefore, it appears that in order to demonstrate the presence of sympathetic vasodilator fibers in normal persons, some other method must be used.

SUMMARY

The mechanism of indirect vasodilatation was investigated, and experiments were carried out to determine the presence of sympathetic vasodilator nerves in the upper and lower extremities of man.

It was shown that indirect vasodilatation induced by warming an extremity depends on the return of the blood from the warmed extremity to the general circulation. It was shown further that the occurrence of indirect vasodilatation in a digit depends on the integrity of its sympathetic nerve supply.

Evidence was obtained in favor of the view that there are sympathetic vasodilator nerves in the upper and lower extremities in man.

Progress in Internal Medicine

SYPHILIS

A REVIEW OF THE RECENT LITERATURE

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The material for this review was selected from publications which appeared during the last half of 1937 and the first half of 1938. As in previous reviews,¹ it has been necessary to exercise a rigid selection of material and largely to exclude the literature on experimental syphilis and on serologic studies.

HISTORY OF SYPHILIS

The effect of social custom and "mass morality" on the usage of words by authors is well illustrated in Sir d'Arcy Power's² discussion of the use of the word pox in English literature. Shakespeare used it nineteen times, but later, during the Victorian era and for many years thereafter, it was taboo. There is no mention of venereal disease in the works of Thackeray or of Dickens.

In an interesting article, the title of which contains the type of pun that would have amused Shakespeare, Stillians³ recounts the controversy between Ricord and Auzias-Turenne over the latter's theory of syphilization. Ricord had stated that animals could not be infected with syphilis. Auzias-Turenne, however, inoculated monkeys, rats, cats, dogs, foxes, rabbits and a goat with pus from venereal ulcers. In some of these animals papules, moist lesions, osseous lesions and other

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1 (a) Moore, J. E. Syphilis. A Review of the Recent Literature, *Arch Int Med* **56** 1015 (Nov.) 1935. (b) Padget, P., and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid* **58**:901 (Nov.) 1936, (c) **60** 887 (Nov.) 1937.

2 Power, d'A. Clap and the Pox in English Literature, *Brit J Ven Dis* **14** 105 (April) 1938.

3 Stillians, A. W. Syphilization. An Episode in the Evolution of Syphilology, *Arch Dermat & Syph* **37** 272 (Feb.) 1938.

manifestations developed which he considered were indicative of syphilis. He observed that repeated inoculation of different portions of the skin with material from the original lesion resulted in successively smaller ulcers, until at last no pustule was formed. Inoculation from a fresh human source would succeed for a time, but after a series of autoinoculations this method also would fail to produce a lesion. He concluded that there was produced an immunity for syphilis comparable to the immunity for smallpox resulting from vaccination and proposed to protect all prostitutes and others professionally exposed to the disease by this method of syphilization.

In an amusing article on the birth of syphilis, Robinson⁴ relates the spread of the disease to the triumphant and poorly resisted march of Charles VIII through Italy. The boudoir replaced the battlefield, and Naples became a vast brothel. The physician Thierry de Hery frankly worshipped Charles as the originator of syphilis. On a pilgrimage to the king's grave at St. Denis, France, he went down on his knees and said to a priest who was standing by, "Charles VIII is a good enough saint for me, he put thousands of francs in my pocket when he brought the pox into France." "Since that time," says Robinson, with more wit than accuracy, "all syphilologists have been rich."

The endless controversy concerning the American origin of syphilis is furthered by Holcomb⁵. From an investigation of source material he feels that misconception has arisen from the perpetuation of incorrect translations of the work entitled "Treatise Against the Bubos or the Serpentine Disease of the Island of Espanola," by Ruiz Diaz de Isla, which was printed in 1539. On retranslation he found no good evidence to support the theory of the American origin of syphilis except a chapter which deals with the use of guaiacum as a specific remedy for the disease. Guaiacum, or holy wood, was native to Haiti and Puerto Rico.

Haltom and Shands⁶ present more tangible evidence on the other side of the controversy. A study of twenty-four specimens of bones which had been unearthed in archeologic investigations at Moundville, Ala., revealed in twenty-one of them changes which were suggestive of syphilis, and in one skull the changes were so characteristic that the authors felt that no other diagnosis was tenable. Archeologically

4 Robinson, V. The Birth of Syphilis, *Arch. Dermat. & Syph.* **36** 325 (Aug.) 1937.

5 Holcomb, R. C. Who Gave the World Syphilis? The Haitian Myth, New York, Froben Press, Inc., 1937.

6 Haltom, W. S., and Shands, A. R. Evidence of Syphilis in Mound Builders, *Arch. Path.* **25** 228 (Feb.) 1938.

there can be no doubt as to the antiquity of the mounds. They are estimated to be no more recent than 1000 A. D. These authors conclude, therefore, that there appears to be sufficient evidence in these specimens to prove that syphilis existed among the mound builders many centuries before the discovery of America by Columbus.

SPIROCHAETA PALLIDA

Quantitation of Experimental Inoculums—There has long been need for a study of the influence of the size of the inoculum on the manifestations of experimental syphilis. This has now been made possible by Morgan and Vryonis,⁷ who describe a satisfactory method for counting the actual number of spirochetes in fluid suspensions.

Morphology—Bessemans⁸ discusses the morphologic variations in the causative organism of syphilis and contends that the discrepancy between his findings and those of others who have not been able to demonstrate the presence of spirochetes in tissues which are infectious does not prove the existence of an infravisible or granular form but is probably a matter of technic. The so-called atypical forms of *S. pallida* he believes to be only fragmented and altered organisms.

Although he maintains that the organism causing syphilis is a morphologic unity, Bessemans⁹ believes that functionally it has innumerable aspects. In support of this view he cites various biologic properties of the spirochete, both in vitro and in vivo, discusses the phenomena of drug resistance and variations in virulence which are said to be produced by repeated passage of the virus through experimental animals and recalls the changes in the clinical manifestations of syphilis which have taken place since the fifteenth century. The theory is ingenious and plausible but, being largely undocumented, is unconvincing.

Nyka¹⁰ continues his argument as to the variability of form of *S. pallida* in experiments made on rabbits infected by means of intratesticular inoculations with spirochetes of the Truffi strain. The iliac and popliteal lymph nodes were examined microscopically. In freshly infected animals he found a few typical spirochetes and many filamentous forms. He concludes that the causative agent of syphilis is a polymorphous virus which exists in two distinctly different forms. (1) the classic

7 Morgan, H., and Vryonis, G. P. A Method for the Quantitation of Inocula in Experimental Syphilis, *Am J Syph, Gonorr & Ven Dis* **22** 462 (July) 1938.

8 Bessemans, A. Morphologic Variations of the Syphilitic Germ, *Am J Syph, Gonorr & Ven Dis* **22** 294 (May) 1938.

9 Bessemans, A. Functional Variations of the *Treponema Pallidum*, *Am J Syph, Gonorr & Ven Dis* **22** 301 (May) 1938.

10 Nyka, W. Nouvelles recherches sur le polymorphisme du virus syphilitique dans les ganglions lymphatiques du lapin, *Ann Inst Pasteur* **60** 316 (March) 1938.

spiral, which he believes to be a transitory form, and (2) a filamentous form, which he still believes, though it seems to us without adequate proof, to be the true infectious form of the syphilitic virus

Staining—Kerr¹¹ discusses modifications of the Warthin-Starry method of staining spirochetes in sections of tissue and attributes the reported failures of some workers to the use of unclean glassware or reagents, a slurring over of technical details and a lack of persistence in searching for the organisms. Steiner¹² describes new and simple methods for staining spirochetes in frozen sections and in smears.

Effect of Low Temperatures—Under natural conditions *S. pallida* and *Treponema pertenu* die soon after removal from a living host. Hitherto strains of these organisms could be maintained for experimental purposes only by inoculating susceptible animals. In a previous communication Turner¹³ described a simple method for freezing and maintaining specimens of tissue containing spirochetes at a temperature of approximately -78°C , thus eliminating the time and expense entailed in propagating spirochetes of syphilis or yaws in animals. In the present communication¹⁴ he shows that after having been frozen and maintained for at least one year at temperatures near -78°C , *S. pallida* and *T. pertenu*, on thawing, exhibited a normal morphologic picture, motility and virulence. At temperatures of -10°C and -20°C , spirochetes of syphilis did not survive as long as two months. That *S. pallida* may survive even much lower temperatures for at least brief periods is reported by Jahnel,¹⁵ who describes experiments showing that the organisms can endure a temperature of -271.5°C for two and one-half hours without losing their virulence.

EXPERIMENTAL SYPHILIS

Seeking further information concerning the pathogenesis of syphilis, particularly syphilis of the nervous system, Stroesco and Vaisman¹⁶

11 Kerr, D. A. Improved Warthin-Starry Method of Staining Spirochetes in Tissue Sections, *Am J Clin Path* **8** 63 (March) 1938.

12 Steiner, G. A New Method for Staining Spirochetes and Bacteria in Smears, *J Lab & Clin Med* **23** 293 (Dec.) 1937, A Simple Method for Demonstration of Spirochetes in Frozen Section, *ibid* **23** 316 (Dec.) 1937.

13 Turner, T. B. The Preservation of Virulent *Treponema Pallidum* and *Treponema Pertenu* in the Frozen State, *J Clin Investigation* **15** 470 (July) 1936.

14 Turner, T. B. The Preservation of Virulent *Treponema Pallidum* and *Treponema Pertenu* in the Frozen State, with a Note on the Preservation of Filtrable Viruses, *J Exper Med* **67** 61 (Jan.) 1938.

15 Jahnel, F. Ueber das Ueberleben von Syphilisspirochäten bei tiefster Temperatur (-271.5°C , 17° vom absoluten Nullpunkt entfernt), *Klin Wchnschr* **17** 837 (June 11) 1938.

16 Stroesco, G., and Vaisman, A. La syphilis expérimentale cliniquement inapparente de la souris, *Ann Inst Pasteur* **59** 403 (Oct.) 1937.

studied experimental syphilis in the mouse. Mice were infected by the implantation of fragments of tissue from fresh rabbit syphilomas into or under the skin. The animals were killed at varying intervals afterward, and their tissues were studied microscopically with the aid of a modification of the Dieterlé technic which the authors describe. Either typical or atypical forms of spirochetes were found to be widely distributed throughout the tissues, including the nervous system. Examination of the area surrounding the site of implantation of the infecting graft, however, they felt gave significant information regarding the mode of infection of the neuraxis. As a result of their studies they concluded that after implantation of an infecting graft the spirochetes at the center of the graft became transformed into stages intermediate between the spiral form and argentophilic granules, while at the periphery they migrated from the graft and invaded the adjoining tissues, where they multiplied without producing atypical forms. Reproduction was around the vessels in the corium, whence the organisms passed along the connective tissue fibers into the nerves, finally to infect the spinal ganglions. In guinea pigs in which primary lesions were produced, each lesion apparently immunized the adjacent epidermis and prevented multiplication of the spirochetes in that region, but the immunization failed to affect the peripheral nerves, in which the spirochetes multiplied and spread.

Vaisman¹⁷ injected spinal fluid from 9 patients with dementia paralytica into mice by the intracerebral and subcutaneous routes. The mice were killed four months later. Examination of the lymph nodes by the Dieterlé method revealed no organisms resembling *S. pallida*. Transfer by means of injecting material from the lymph nodes into rabbits likewise gave negative results.

Although the author tends to accept these observations as conclusive evidence that the cerebrospinal fluid of patients with dementia paralytica is not infectious, the notorious variability of the mouse in experimental studies of syphilis makes the findings of little value.

Influence of Sex and Sex Hormones—Kemp, Shaw and Fitzgerald¹⁸ have interested themselves in the important problem of the relation of sex hormones to the course of experimental syphilis. As a part of this study they examined the effect of placental extract on the course of experimental syphilis in the rabbit. A crude placental extract, containing little or none of the immune substance effective in the

17 Vaisman, A. Le liquide céphalorachidien des paralytiques généraux est-il virulent? *Compt rend Soc de biol* **124** 1166, 1937.

18 Kemp, J. E., Shaw, C., and Fitzgerald, E. M. The Effects of Placental Extract on the Course of Experimental Rabbit Syphilis, *Am J Syph, Gonorr & Ven Dis* **22** 368 (May) 1938.

prevention and abortion of measles and only a small amount of estrogenic substance, had no influence on the course of the infection. A commercial placental extract (placimmunin) prepared according to the method of McKhann, known to be effective in the prevention and abortion of measles, had a favorable effect in 8 of 12 animals that survived treatment. As yet, however, the significance of these observations cannot be interpreted.

The same authors¹⁹ report a comparative study of the course of experimental syphilis in normal male and female rabbits and in male and female rabbits treated six days a week for twenty-one weeks with 20 international units of estrogen (in the form of theelin in oil) and observed for one hundred and fifty-seven days after the inoculation. Their findings suggested that estrogenic substances might have been a factor responsible for the milder course of syphilis in normal female rabbits and the modified course of the disease in female rabbits which became pregnant simultaneously with the infection.

As another part of the same group of studies Kemp and Shaw²⁰ observed the effects of castration on the course of experimental syphilis in male and female rabbits and reported the following results: 1 The syphilitic infection was milder in normal female than in normal male animals, as shown by a less severe reaction at the site of inoculation and the development of fewer generalized lesions. 2 In addition to a more marked reaction at the site of inoculation, the course of the syphilitic infection was more severe in normal males than it was in castrated males. 3 As judged by the occurrence of generalized lesions, the infection was milder in castrated females than in normal females. 4 The favorable influence of castration on the course of experimental syphilis was approximately the same for male and female rabbits.

IMMUNITY IN SYPHILIS

Kolmer²¹ discusses at length the question of serologic reactions and immunity in relation to infection and treatment of syphilis. He believes that reagin is a product of infection with *S. pallida*, although it is not of itself spirocheticidal or spirochetistatic. Nevertheless it is not without immunologic significance, since its persistence in chronic syphilis after one or two years of modern therapy indicates, on the

19 Kemp, J. E., Shaw, C., and Fitzgerald, E. M. The Effect of the Administration of Theelin upon the Course of Experimental Rabbit Syphilis, *Am J Syph, Gonorr & Ven Dis* **22** 9 (Jan) 1938.

20 Kemp, J. E., and Shaw, C. The Effects of Castration upon the Course of Experimental Syphilis in Male and Female Rabbits, *Am J Syph, Gonorr & Ven Dis* **22** 133 (March) 1938.

21 Kolmer, J. A. Serologic Reactions and Immunity in Relation to Infection and Treatment of Syphilis, *Am J Syph, Gonorr & Ven Dis* **22** 426 (July) 1938.

basis of clinical evidence, that sufficient tissue immunity may be present to protect the patient against progression or relapse of the syphilitic infection. Though he grants that persistence of reagin may indicate immunity, he nevertheless feels that in cases of both early and chronic syphilis, including latent, benign (cutaneous and osseous) and visceral infections, the persistently positive serologic reactions are not usually due to reagin remaining after biologic "cure" but are evidence of persistence of the infection. While proof of either point of view remains unobtainable, Kolmer takes the position that for the patient who manifests seroresistance, periodic courses of follow-up therapy after initial treatment for one to two years are desirable to guard further against clinical relapse or progression of the disease.

LISI²² shows that immunity is not established in rabbits after scrotal, subcutaneous and intraperitoneal injections of an emulsion of material from syphilitic lesions which previously has been rendered avirulent by heating. When injections of a virulent virus were given to vaccinated animals the lesions were larger and the period of incubation was shorter than when the injections were given to control animals, suggesting that a greater local sensitiveness to the spirochete was established in the vaccinated animals. The possibility that this heightened reaction might be due to general tissue sensitivity produced by the previous injection was not considered.

Beck²³ examined fifteen specimens of serum and two specimens of cerebrospinal fluid from human beings and three specimens of serum from syphilitic rabbits by a quantitative *in vivo* method for the presence of antibodies protective against the spirochete of syphilis. No evidence of such antibodies was found. Observation *in vitro* did not reveal phagocytosis of the organism.

SEROLOGY

As in previous years,¹ space cannot be given to the many articles dealing with the technic of serologic tests for syphilis or to those comparing one test with another. It is desirable, however, briefly to refer to certain papers which aid in clarifying in the minds of practicing physicians the interpretation of these tests.

It is obvious that the reliability of the serologic report which a laboratory supplies to a physician depends on two factors: the theoretic sensitivity and specificity of which the test employed is capable in expert hands and, more important, the actual sensitivity and specificity of the test as it is performed in the laboratory which is making the report.

22 LISI, F. Ricerche sperimentali sulle reazioni immunitarie all'inoculazione di materiale sifilitico virulento in conigli preventivamente trattati con estratti di sifiloma, *Gior ital di dermat e sif* **78** 691 (Aug) 1937.

23 Beck, A. The Occurrence of Protective Antibodies in Syphilis, *J Path & Bact* **44** 399 (March) 1937.

The first consideration has been dealt with in previous reports¹ of the Committee on Evaluation of Serodiagnostic Tests for Syphilis. A comparative study of the efficiency of the performance of serodiagnostic tests for syphilis in thirty-nine state laboratories is reported by Parran and his associates²⁴. Each health officer was asked to designate the test whose performance he desired to have evaluated, and the tests specified determined the choice of four private control laboratories. A study of the tables and graphs obtained from the sixty-nine serologic tests on each specimen of blood submitted revealed the fact that some of the state laboratories are not qualified to perform efficient diagnostic service or to inaugurate any system of licensure involving approval of local laboratories within their respective states. In many states, however, the efficiency of the performance of the tests was maintained at a high level. It was also evident that the routine employment of a single serodiagnostic test, even though performed by competent workers, is occasionally unreliable. The recommendations of the committee should receive immediate study. It was advised that provision be made for adequate training of state and local laboratory technicians in the laboratories of the originators of the methods employed and that in the future only a thoroughly competent technical personnel be employed. A system of periodic inspection of state laboratories by thoroughly trained serologists of the United States Public Health Service should be devised and made available. The facilities for the special study of serologic methods in the Venereal Disease Research Laboratory of the United States Public Health Service on Staten Island in New York should be utilized to a greater extent. Periodic comparative examination of the performance of serodiagnostic tests is desirable. Finally, the committee advised that full advantage be taken of existing local laboratory facilities and that provisions be made to approve and subsidize qualified local laboratories for the performance of diagnostic services in the control of syphilis²⁵.

Hazen²⁶ reemphasizes the imperative need for the efficient performance of serodiagnostic tests and points out the opportunity which the serologic conferences sponsored jointly by the United States Public Health Service and the American Society of Clinical Pathologists pro-

24 Parran, T., Hazen, H. H., Mahoney, J. F., Sanford, A. H., Senear, F. E., Simpson, W. M., and Vonderlehr, R. A. Serodiagnostic Tests for Syphilis as Performed by Thirty-Nine State Laboratories. A Comparative Study, Report of the Committee on Evaluation of Serodiagnostic Tests for Syphilis, *J. A. M. A.* **109** 425 (Aug 7) 1937, *Ven. Dis. Inform.* **18** 273 (Aug.) 1937.

25 Serodiagnostic Tests for Syphilis in State Laboratories, Current Comment, *J. A. M. A.* **109** 437 (Aug 7) 1937.

26 Hazen, H. H. Syphilis Control. The Need for Efficiently Performed Serodiagnostic Tests, *Journal-Lancet* **58** 127 (March) 1938.

vide to state health officers to evaluate the quality of the work done in their several serologic laboratories. To aid in improving the quality of serodiagnostic tests for syphilis, he makes certain specific recommendations. Only certified technicians should be employed, medical students should be trained in the collection of blood, private physicians should ascertain whether the laboratories they use employ methods which have been evaluated by the United States Public Health Service, health officers should be urged to have their laboratories participate in the evaluation projects, and the opportunities for evaluation by a state laboratory should be available to other laboratories in the state. These recommendations should be followed by every laboratory which attempts the serodiagnosis of syphilis, and it should be the privilege of the practitioner who submits samples of blood for examination to be assured that they are carried out.

Nagle and Willett²⁷ collate the information which has been made available by the five serologic conferences and state the following conclusions:

The foundation for the selection of suitable standard tests used in the serum diagnosis of syphilis has been laid by data accumulated regarding the efficiency of 46 Wassermann and 54 precipitation tests in five official projects.

From this compilation it is obvious that a serologic test can possess as a minimum 99 per cent specificity (excepting certain few diseases, especially malaria and leprosy) and 65 per cent sensitivity. These percentages should be considered the base line, and tests conforming to these standards should be used in diagnostic laboratories. Tests not conforming to these standards should be used only experimentally until they are adjusted to meet these standards. Tests having high sensitivity might be used as presumptive or exclusion tests, even though lacking in specificity.

It is hoped that tests which at present fit in with these standards will be improved to increase both sensitivity and specificity. That this can be done, especially in regard to sensitivity, was demonstrated by diagnostic laboratories with Kahn, Kolmer and Kline tests in Project 5.

The Laughlen Test—The Laughlen test has been presented as a reliable test for syphilis which can be performed in a few minutes, which requires little equipment, which is inexpensive and which can be done by any medical practitioner or technician without special training.²⁸ Usher²⁹ says, however:

In the hands of the author, the Laughlen test gave a prohibitive number of positive reactions in a presumably nonsyphilitic population. When the sensitivity

27 Nagle, N., and Willett, J. C. What Did Five Official Evaluation Studies of Tests for Syphilis Reveal? *Am J Syph, Gonorr & Ven Dis* **22** 231 (March) 1938.

28 Laughlen, G. F. A Rapid Test for Syphilis, *Canad M A J* **33** 179 (Aug.) 1935.

29 Usher, G. S. An Appraisal of the Laughlen Serologic Test for Syphilis, *Am J Syph, Gonorr & Ven Dis* **22** 452 (July) 1938.

of the reagent was reduced sufficiently to eliminate these falsely positive reactions, it failed in a significant number of instances to detect reagin in sera which were positive to the Eagle flocculation reaction

It is concluded that the Laughlen serologic test for syphilis may be of value in a reliable laboratory as a spot or exclusion test but is not a satisfactory test to be used by a "medical practitioner or technician without special training" (as claimed by Laughlen)

Other investigators have agreed with Usher. From a comparison of the Laughlen test with a complement fixation test of 1,500 specimens of serum, Churg, in discussing a report made by Chargin,³⁰ concludes

In its present form the Laughlen test is not a reliable procedure and should not be employed

Sobel³¹ says

The sensitivity of this test was hardly equal to that of the Wassermann test

Laughlen states that it is an office procedure, yet we found that we had to discard the results in the first 300 tests because we lacked the experience for their accurate performance. The Laughlen test at the present time is not suitable for use by the average practitioner. It is still a laboratory procedure

Rein³² says

I believe that new tests of this type should not be publicized and sold to practitioners until their specificity and sensitivity are accurately determined by reliable serologists

Editorial writers also agree in condemning the suggestion that serologic tests for syphilis may be made an office procedure.³³

The publications of the Committee on the Evaluation of Serologic Tests for Syphilis indicate that all too frequently both complement fixation and flocculation tests are carried out at a level of efficiency below that of which the tests are inherently capable. It is alarming that some commercial concerns are offering for sale to general practitioners relatively new and unestablished serologic test outfits containing antigen and other materials. The promoters claim that these methods may be carried out by the practitioner in his office, are suitable for rapid diagnostic work with whole blood and with spinal fluid and are sufficiently accurate to guide any physician in the treatment of his patients with syphilis. The fact that the antigens for these methods are crude or that they may deteriorate rapidly is not mentioned. Neither is it pointed out that dye materials incorporated in the antigens are useless to a trained serologist and will be equally valueless to one not familiar with the interpretation of flocculation reactions. Warning is not given of the danger which is always present in serologic procedures carried out with whole blood or of the complete reversal which inactivation may induce. Nor is it admitted that these methods have had only a limited practical test in hands other than those of the originators. Furthermore, a most grievous omission is the failure to recommend the use of positive and negative control serums as

30 Chargin, L. Asymptomatic Syphilis Associated with a Positive Wassermann and a Negative Laughlen Test, *Arch Dermat & Syph* **37** 856 (May) 1938

31 Sobel, N, in discussion on Chargin³⁰

32 Rein, C R, in discussion on Chargin³⁰

33 New Serologic Tests for Syphilis, *Current Comment*, J A M A **110** 1373 (April 23) 1938

guides in the interpretation of the test. The care of the glassware, the concentration and p_H of the salt solution and many other factors requisite for trustworthy serologic results are omitted from the instructions. Thus, active commercial promoters may place in the hands of the individual physician everywhere a diagnostic function which is acceptable as efficient only when performed in laboratories adequately equipped and staffed by trained personnel. The claims for these techniques are based on inadequate experience and the procedures themselves are open to criticism on many technical grounds. The science of serology has not as yet progressed to a degree of simplicity at which the detection of syphilis may be placed on a basis comparable to the detection of albumin in the urine. It is difficult to see how any premature steps in this direction can do other than work to the detriment of the patient with syphilis.

The Hinton Test—Because there has been controversy regarding the value of a negative reaction of the Hinton test of the blood in excluding neurosyphilis, Marquis³⁴ reviewed the records of 621 consecutive patients with syphilis for each of whom had been made at least one Hinton test, one test of the complement fixation reaction of the blood and an examination of the cerebrospinal fluid. Serologic tests of the cerebrospinal fluid for syphilis gave a positive reaction for 172 (28 per cent) of this group and a doubtful reaction for 4 others. The Hinton test of the blood gave a negative reaction in 11 cases in which the Wassermann test of the spinal fluid gave a positive reaction. The Hinton test is described as "fluctuating" in 6 other cases. In 1 case in which the Wassermann test of the spinal fluid gave a doubtful reaction, the Hinton test gave a positive reaction, in 1 case it gave a doubtful reaction and in 2 cases it gave a negative reaction.

In his discussion the author presents brief reports of the 13 cases in which a negative reaction to the Hinton test of the blood and a positive or doubtful complement fixation reaction of the cerebrospinal fluid were obtained in order to show that in all these cases neurologic abnormalities were manifest which in themselves would demand examination of the cerebrospinal fluid to clarify the diagnosis. He concludes:

It would appear from this study that routine lumbar punctures may be safely omitted in patients with syphilis who have no clinical evidence of central nervous system disease and who have a persistently negative Hinton test of the blood. It seems equally evident, however, that whenever there are signs or symptoms of central nervous system injury or whenever there is a persistently positive Hinton test, spinal fluid examination cannot be safely omitted.

Positive Results of Serologic Tests of Normal Animals—For several years evidence has been accumulating that a high proportion of normal animals of various species other than man may give a positive reaction to serologic tests for syphilis. Further confirmation of this

34 Marquis, H. H. The Hinton Test of the Blood in Neurosyphilis, *Am J Syph, Gonorr & Ven Dis* **22** 208 (March) 1938.

fact is offered by Greene, Harding, Hudspeth and Pistor,³⁵ who performed Kahn, Kline, Ide, Eagle and Laughlen tests on blood from dogs, rabbits, goats, horses, sheep, chickens and cows. Though these serums showed a relatively high percentage of positive reactions, the different tests gave widely varying results. The Kline and Laughlen tests gave the highest and the Ide and Eagle tests the lowest percentage of positive reactions.

The presence of a reagin-like substance in the blood of normal animals has, in our opinion, received inadequate consideration by clinicians and serologists. Is it not possible that what is true in a high proportion of other animals may also be true in at least a small proportion of human beings and that an unsupported positive reaction to a serologic test, even if adequately checked against technical error, may sometimes represent a normal biologic peculiarity rather than the presence of syphilitic infection? Further study of this important point is urgently needed.

Mackie and Watson,³⁶ Porro,³⁷ Manteufel and Beger,³⁸ Furst³⁹ and Eagle⁴⁰ have reported results similar to those of Greene and his collaborators, but there have been no reports of studies calculated to identify the substance which produces the positive reaction.

That fears as to the validity of a positive reaction to a serologic test may, however, be more apparent than real and that biologic false positive reactions, if they occur at all, must be rare is suggested by the serologic surveys of college students carried out in Wisconsin and Minnesota. At the University of Wisconsin⁴¹ "a total of 3,389 tests was done on 30.5 per cent of the student population. . . a negligible amount of syphilis was found." Only 6 students showed a

35 Greene, R. A., Harding, H. B., Hudspeth, W. T., and Pistor, W. J. The Reaction of the Sera of Different Animals to the Kahn, Kline, Ide and Laughlen Tests, *J. Lab. & Clin. Med.* **23** 763 (April) 1938.

36 Mackie, T. J., and Watson, H. F. On the Immunological Nature of the Principle in Serum Responsible for the Wassermann Reaction, with Reference Also to the Flocculation Reaction of Sachs and Georgi, *J. Hyg.* **25** 176 (July) 1926.

37 Porro, T. J. The Kahn Reaction with Serum of Different Animals, *J. Infect. Dis.* **53** 210 (Sept.) 1933.

38 Manteufel, P., and Beger, H. Die Serodiagnose der Kaninchensyphilis, *Deutsche med. Wchnschr.* **50** 269 (Feb. 29) 1924.

39 Furst. Zur Frage der Natur der komplementbindenden Stoffe in positiven tierischen und luetischen menschlichen Seris bei der Wassermannschen Reaktion, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **23** 358, 1914.

40 Eagle, H. Studies in the Serology of Syphilis. VI. The Induction of Antibodies to Tissue Lipoids (a Positive Wassermann Reaction) to Normal Rabbits, *J. Exper. Med.* **55** 667 (April) 1932, Laboratory Diagnosis of Syphilis, St. Louis, C. V. Mosby Company, 1937, p. 302.

41 Cole, L. R. Survey of Syphilis Among Students at University of Wisconsin, *Arch. Dermat. & Syph.* **38** 70 (July) 1938.

positive and 6 a doubtful reaction to serologic tests for syphilis. Boynton and Davies⁴² report that during the past ten years serologic tests for syphilis have been performed on about 19,000 students at the University of Minnesota. In only 39 (0.2 per cent) of the cases were persistently positive reactions found.

Rothbart⁴³ contends that fluctuations in the serologic reactions of presumably healthy children of normal healthy parents are occasionally observed. He presents a report of 12 apparently nonsyphilitic children, observed during the past two years, for whom the Kahn test gave a positive reaction on one or more occasions. Later the reactions became negative in 11 of the 12 cases. Infection, either acute or chronic, was present in 11 of the 12 cases.

Provocative Method—According to Rajka,⁴⁴ antibodies in cases of syphilis are produced in the reticuloendothelial system. The Wassermann test of the blood, therefore, may give a negative reaction even though antibodies are stored in the tissues. Theoretically it should be possible to drive these "stored" antibodies from their sites of production into the blood in order to bring about a positive reaction to serologic tests for syphilis. Pressor substances have been employed for the purpose, but for the antibodies to reach the blood there must be vasodilatation after the vasoconstriction. By combining epinephrine, ephedrine and muscle extract, Rajka prepares a substance which he calls "provocaine." This is injected intramuscularly after a specimen of blood has been taken for testing, and additional specimens are taken one-half hour and one hour later. He believes that this method of testing is a valuable aid in proving that a "cure" has been achieved.

Twenty-five normal controls showed no change of the negative reaction either to a Bordet-Wassermann or to a precipitation test. For patients known to have syphilis, a variety of results was observed. The Bordet-Wassermann test was used for 581 patients, also 412 were tested by means of flocculation tests. Of the patients in the former group, 367 gave a negative reaction before the test, for 334 of these patients the reaction to the Bordet-Wassermann test remained negative, but it became positive for 33 (9 per cent of the group). There were 214 patients who gave a positive reaction to the Bordet-Wassermann

42 Boynton, R. E., and Davies, B. P. The Routine Wassermann Test in College Students, *Journal-Lancet* **58** 134 (March) 1938.

43 Rothbart, H. B. The Variability of the Kahn Reaction in Children, *J. Pediat* **11** 483 (Oct.) 1937.

44 Rajka, E. Sur la question des provocations serologiques dans la syphilis a l'occasion d'une nouvelle methode de provocation, *Ann. de dermat. et syph.* **8** 624 (Aug.) 1937.

test before the "provocative" test was made. The reaction remained unchanged for 109 of them, and it increased in strength for 45 and decreased in strength for 60.

The results for a group of 412 patients with respect to a flocculation test were somewhat similar. The reaction before the "provocative" test was positive in 158 cases and negative in 254. In 13 cases (5 per cent) in which the reaction had been negative it became positive. Of the 158 cases in which positive reactions were obtained originally, the reaction remained unchanged in 116, and it became more strongly positive in 12 and less strongly positive in 30.

Cerebrospinal Fluid—Kraus⁴⁵ claims that the Takata-Ara test is a rapid, simple and reliable colloid test that can be used in outpatient clinics for the diagnosis of neurosyphilis. Richter⁴⁶ advocates a modification of the colloidal gold test which makes possible the reading of the results after one hour, instead of after twenty-four hours. Reibeling⁴⁷ is of the opinion that the hydrochloric acid-collargol reaction of the cerebrospinal fluid is determined by the hydrolysis of proteins. He believes that this test gives a curve characteristic of dementia paralytica which is not the case with the other colloidal tests. In about 50 cases of latent syphilis without involvement of the central nervous system the test gave normal curves. In a few cases in which there was only slight involvement of the central nervous system, the curves promptly became positive. For treated patients with dementia paralytica, tabes dorsalis or latent syphilis the test proved to be a good indicator of active syphilitic involvement of the central nervous system.

THE SOCIAL AND PUBLIC HEALTH ASPECTS OF SYPHILIS

Although an appeal was made by Marion Sims in 1876 for attention to venereal diseases, the first really effective steps were taken by Herman Biggs, of New York, in 1912. He advocated the reporting of cases and free serologic testing and said he felt that special clinics and hospital facilities for patients with venereal diseases should be established.⁴⁸

Official Attitudes—In the light of the fears expressed that a concerted effort directed toward the control of syphilis would serve as the

45 Kraus, M. Die Takata-Ara-Reaktion (Einglas Methode) in der ambulanten Praxis der Neurolues, *Klin Wchnschr* **16** 1815 (Dec 25) 1937.

46 Richter, J. Zur Goldsolreaktion, *Ztschr f Hyg u Infektionskr* **120** 219 (Dec 21) 1937.

47 Reibeling, C. Die Salzsäure-Collargol-Reaktion, eine neue Liquorreaktion, *Klin Wchnschr* **17** 783 (May 28) 1938.

48 Biggs and the Control of Syphilis, editorial, *Quart Bull*, City of New York Dept Health **5** 63 (Aug) 1937, abstracted, *Ven Dis Inform* **19** 97 (April) 1938.

opening wedge for the establishment of "socialized medicine," the comments of the president (1937-1938) of the American Medical Association⁴⁹ are in order. In his opinion the present concern about public health has had a dual origin: first, the progress which has been made in preventive medicine and, second, the awakening of the national consciousness to the deplorable wastefulness of illness.

With regard to syphilis, two factors make the outlook favorable. Treatment of the patient does not necessitate that he give up work, and a specific cure may be obtained in the early stage of the disease.

In order to develop the opportunity, there are three points to be considered. First is the education of the public. The second great objective is the arousing of the medical profession generally. Third is the matter of the cost of treatment.

The middle class, especially those on the borderline of "medical indigency," present a serious phase of the problem. Many of them refuse to go to a clinic. Taking the long view, Upham believes that medical societies should not temporize but should meet the issue squarely.

The surgeon general of the United States Public Health Service is in complete agreement.⁵⁰ Specifically, he makes basic recommendations for the development of adequate facilities for the control of syphilis as follows:

There should be a trained public health staff to deal with syphilis in each state and city.

Minimum state laws should require reporting of cases, follow up of delinquents, and the finding of source of infection and contacts.

Premarital medical certificates, including serodiagnostic tests, should be a legal requirement.

Diagnostic services should be freely available to every physician without charge and should meet minimum state standards of performance.

Treatment facilities should be of good quality, with convenient hours and location. Wherever possible the clinic service should be a part of an existing hospital dispensary. Hospital beds should be provided for patients needing bed care.

The states should distribute antisypilitic drugs to physicians for the treatment of all patients.

Routine serodiagnostic tests need to be used much more widely. In particular, every pregnancy, every hospital admission, every complete physical examination should include this test.

The informative program in modern diagnosis, treatment, and control should be prosecuted vigorously among physicians and health officers, especially through the use of trained consultants.

The public educational program must be persistent, intensive, and aimed especially at those individuals in the age groups in which syphilis is most frequently acquired.

49 Upham, J. H. J. The Private Physician's Part in the Syphilis Campaign, *J. Social Hyg.* **24** 134 (March) 1938.

50 Parran, T. Control of Syphilis, (a) *J. A. M. A.* **109** 205 (July 17) 1937, (b) *Ven. Dis. Inform.* **18** 223 (July) 1937.

The Private Physician and the Control of Syphilis—The importance of the practitioner's part in the control of syphilis has had great emphasis. Clarke⁵¹ says that in the city of New York the practicing physicians are more valuable with regard to the control of syphilis than all the many clinics and hospitals, voluntary and official. Jeans⁵² feels that in the control of prenatal syphilis appropriate regulations by the state department of health and cooperation in their enforcement are most important. Casselman⁵³ states

To control venereal disease various services should be more readily available. The health departments should provide free laboratory service, free drugs, free follow-up service and a limited amount of free consultation service. Because much of the public health work in syphilis must be done by private physicians, some financial provision for this work must be made by health departments.

The Incidence, Prevalence and Trend of Syphilis in Chicago—Usilton and her collaborators⁵⁴ present a study of the problem of syphilis in Chicago which was made possible by the cooperation of all the clinics for syphilitic patients and 99.6 per cent of the practicing physicians of that city. They found that there are 14,350 patients with syphilis constantly under medical care in Chicago (44 per ten thousand of the population). More than 15,000 residents of Chicago seek treatment for syphilis each year, but only 2,500 of them have early syphilis. Of the latter group, 23 per cent of the private patients and 52 per cent of the clinic patients receive minimal effective treatment before lapse or discharge. Few of the patients with late syphilis have had treatment for early syphilis. During the period of study there was an increase in the number of patients with late syphilis who sought private medical care.

Syphilis and Industry—Certain branches of the federal government and some industrial organizations now require a routine serologic test for syphilis of all applicants for positions and refuse employment to those whose tests give positive results. The reasons that have been assigned for these regulations are: 1. There is danger of transmission of syphilis, especially by food handlers. 2. A syphilitic person who uses dangerous machinery is a hazard to himself and to others. 3. There is additional financial risk to the company, because the employee may become disabled on account of syphilis and because courts have awarded

51 Clarke, C. W. The New York City Plan for Combating Syphilis, J. A. M. A. **109** 1021 (Sept. 25) 1937.

52 Jeans, P. C. Cooperation of the Private Physician in the Control of Prenatal Syphilis, Ven. Dis. Inform. **19** 93 (April) 1938.

53 Casselman, A. J. Service Provided Physicians by the Health Department, Ven. Dis. Inform. **19** 159 (June) 1938.

54 Usilton, L. J., Hunter, H., and Vonderlehr, R. A. Prevalence, Incidence and Trend of Syphilis in Chicago, J. A. M. A. **110** 864 (March 19) 1938.

industrial compensation for injuries aggravated by preexisting syphilis Moore⁵⁵ has voiced objection to such a policy. A positive reaction to a routine serologic test for syphilis should not be a criterion for refusal to hire or for dismissal of an employee. The danger of transmission of syphilis through contact other than sexual is slight. If the infection is old there is little or no danger. There are only two types of syphilis which are likely to cause industrial accidents, namely, cardiovascular syphilis and neurosyphilis (of the latter, especially the paralytic type). The diagnosis of these conditions can be established only by careful study of the physical status of the patient and in cases of neurosyphilis only by examination of the cerebrospinal fluid. If a hazardous occupation is involved and if the applicant gives a positive reaction to a serologic test for syphilis, a careful study should be made, if cardiovascular syphilis and neurosyphilis are excluded, employment should be granted or continued, provided adequate treatment is available. Syphilitic persons who are physically able to work should be allowed to do so.

Russell⁵⁶ also condemns the policy of discharging an employee when it is discovered that he is infected with syphilis and recommends retaining him, provided adequate treatment is taken.

Life Expectancy of the Syphilitic Person—In spite of these condemnatory opinions, Usilton and Miner⁵⁷ provide observations which if confirmed by a larger experience will serve amply to justify the refusal of an employer who provides a pension system or retirement allowances to employ a person with syphilis. Utilizing the material of the Cooperative Clinical Group for actuarial study, these authors determined the death curve for men with acquired syphilis in contrast to the death curve for men of the general population. They found that the "life expectancy of males with acquired syphilis is shortened from that in the general population from ages 30 to 60 years by 17 per cent in the white males and 30 per cent in the Negro males." Charts 1 and 2 give the curves for the mortality rate and the complete expectation of life, respectively, for white men with syphilis and for white men of the general population.

The Epidemiology of Syphilis—Baker⁵⁸ contributes a discussion of the responsibilities of the follow-up worker. Two primary responsi-

55 Moore, J. E. Syphilis in Industry, West Virginia M. J. **34** 97 (March) 1938, Syphilis and Unemployment, J. Indust Hyg & Toxicol **19** 189 (May) 1937.

56 Russell, A. E. The Control of Syphilis in Industry, J. Social Hyg **24**: 10 (Jan) 1938.

57 Usilton, L. J., and Miner, J. R. A Tentative Death Curve for Acquired Syphilis in White and Colored Males in the United States, Ven. Dis. Inform **18**:231 (July) 1937.

58 Baker, E. M. Scope of Activities of Follow-Up Worker, Ven. Dis. Inform **19** 163 (June) 1938.

bilities, she says, are tracing sources of infection and contact and keeping infectious patients under treatment until they can no longer transmit the disease

Ingraham⁵⁹ reports fifteen years' experience with "contact-tracing and case-holding" in New Jersey. He found that

the employment of a confidential persuasive approach to elicit a voluntary response from the patient, in the hands of a trained individual, is about half again as productive of usable epidemiologic information as is the untrained coercive approach. The voluntary response method is likewise superior to compulsive methods in persuading the average suspected contact to submit to medical examination and to about the same degree. In clinic practice women are apparently more apt to

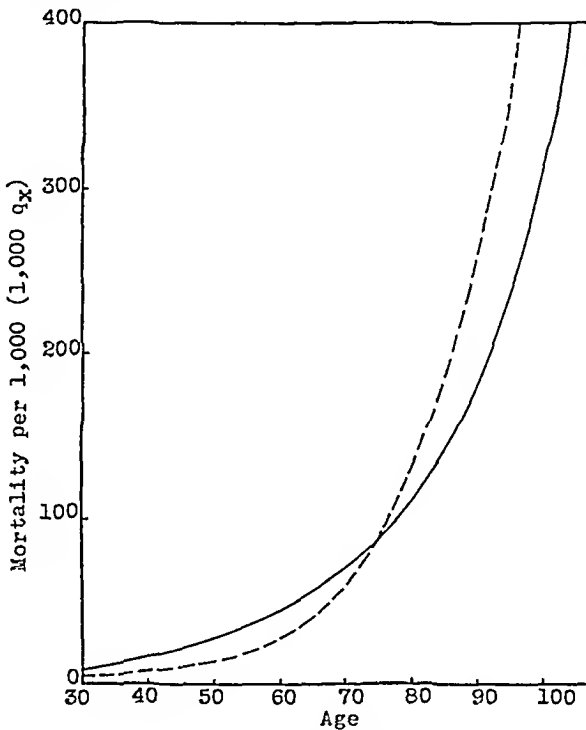


Chart 1—Rate of mortality per thousand for white men with acquired syphilis and for white men of the general population, 1929 to 1931 (from Usilton and Miner⁵⁷). The solid black line indicates data for syphilitic white men, the dash line, data for all white men.

give usable epidemiologic information than are men, and the colored are more cooperative than the white, though the personality of the interviewer doubtless affects these responses considerably.

Organization of a Clinic for Patients with Syphilis—With the establishment of numerous new clinics throughout the country it becomes necessary to consider the administration, location, policies, management, physical equipment and personnel standards of each. In a timely article

⁵⁹ Ingraham, N. R. Syphilis Epidemiology Applied. Fifteen Years' Experience with Contact-Tracing and Case-Holding in New Jersey, *Ven Dis Inform* 19 61 (March) 1938.

Dixon⁶⁰ suggests means of increasing the efficiency of a clinic. He points out that "much of the failure of clinic service is due to acceptance of assignments by physicians who either cannot or will not fill them." He stresses the importance of having the proper person at the admitting desk.

The person who occupies this important position must have uncommon ability to understand not only the requirements of the clinic but all the vagaries of human emotions and conduct in persons who find themselves confronted with a serious situation. Field service for follow-up of delinquents is inversely proportional to the intelligent handling of the patient in the clinic. A smile in the clinic is worth two automobiles in the field.

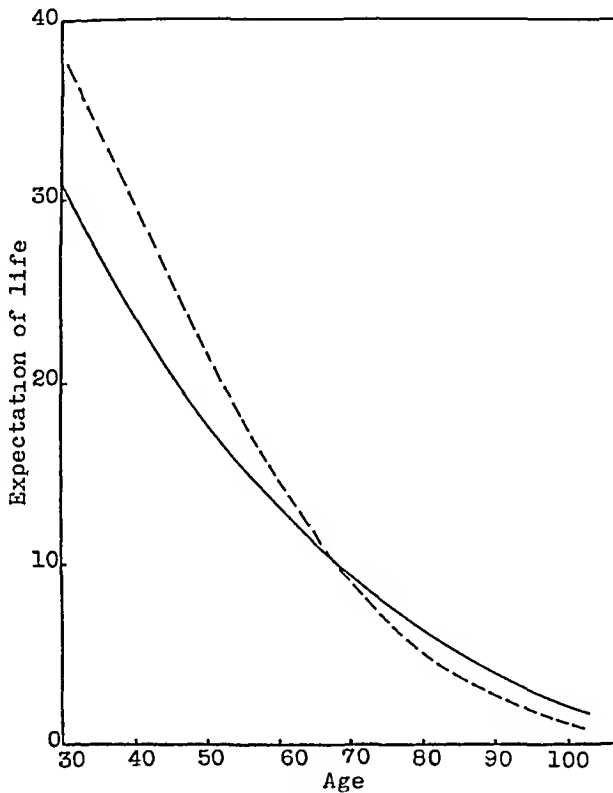


Chart 2—Complete expectation of life for white men with acquired syphilis and for white men of the general population, 1929 to 1931 (from Usilton and Miner⁵⁷). The solid black line indicates data for syphilitic white men, the dash line, data for all white men.

Funds for Syphilis Control—An editorial writer⁶¹ anticipates that congressional appropriations for the control of venereal disease may in the future be decreased rather than increased and urges each public

⁶⁰ Dixon, R. S. The Administration, Location, Policies, Management, Physical Equipment and Personnel Standards of a Syphilis Clinic, *Am J Syph, Gonorr & Ven Dis* **21** 634 (Nov) 1937.

⁶¹ Local Funds for Syphilis Control, editorial, *Am J Syph, Gonorr & Ven Dis* **21** 704 (Nov) 1937.

health officer to approach the program of syphilis control from the standpoint of the problem of the local community

He should make every effort to determine the incidence and prevalence of syphilis in his own community, the dollars' and cents' cost of hospital maintenance of the cardiovascular and neurosyphilitic cripple, and the dollars' and cents' cost of the establishment of an adequate control program in his own city, county, or state. These data should then be presented with all the force at his command to the local governmental appropriating body, the City Council, the County Commissioners, the State Legislature

The passage of the La Follette-Bulwinkle bill⁶² provides for the study of measures for the control of venereal disease and an expansion of the program for venereal disease control. It authorizes appropriations to the amount of \$3,000,000 for the fiscal year beginning July 1, 1938, \$5,000,000 for the year 1939 and \$7,000,000 for the year 1940 and thereafter, and such sums annually as Congress may determine for the purposes of the act. The funds are to be expended by allocation to states, under the direction of the surgeon general of the United States Public Health Service. For the fiscal year 1939 he has announced that 80 per cent of the total amount (viz, \$2,400,000) shall be allotted to the states as follows: 24 per cent on the basis of population, 32 per cent on the basis of the extent of the problem of venereal disease and 24 per cent on the basis of the financial needs of the state. The regulations require that the funds allotted on the basis of population must be matched by old or new appropriations. Provision is made in the act for the training of personnel, and the objective is to make available in every state by Jan. 1, 1940, generally accepted minimal services for the control of venereal diseases.

Training Opportunities in Syphilis Control—In his address on the control of syphilis at the 1937 meeting of the American Medical Association Parran^{50a} gave as a basic principle

There should be a trained public health staff to deal with syphilis in each state and city

It was agreed by the Annual Conference of State and Territorial Health Officers that

- This public health staff must comprise three categories of physicians
- (A) Venereal disease control officers of state and municipal health departments
 - (B) Physicians specially trained in the clinical aspects of syphilis
 - (C) Private practitioners

The need of additional training facilities for all three of these groups, and especially for the first two, was recognized and has now been met. Postgraduate courses in venereal disease training have been organized by practicing physicians and health officers at the Universities of Harvard, New York, Pennsylvania,

62 An Act to Impose Additional Duties upon the United States Public Health Service in Connection with the Investigation and Control of the Venereal Diseases, Public Law 540, 75th Congress of the United States, approved May 24, 1938

Johns Hopkins, Vanderbilt, Howard, Western Reserve, and California. The well-organized course at Howard University is especially for Negro physicians.⁶³

In discussing the training of a venereal disease control officer, Turner⁶⁴ emphasizes the necessity for combined public health and clinical knowledge and points out that although training in the clinical and field aspects of syphilis can be obtained by actual work in clinics and in public health departments, the same amount of training can be secured in a shorter period and with less effort through the medium of organized courses in universities. Such courses should extend over a period of not less than six months and preferably of one year. The work should be largely practical, with a minimum of didactic instruction.

DRUGS

Neoarsphenamine—Harrison and Probey⁶⁵ studied the effect of moisture and age on the stability of neoarsphenamine. Samples of the drug, which had been submitted as a routine to the National Institute of Health for official testing, were examined after storage for varying periods at a temperature of about 20 C. The moisture content was determined by drying over phosphorus pentoxide, and the stability was judged from the appearance of a 10 per cent solution. They found that deterioration is directly proportional to age and moisture content but that neoarsphenamine containing not more than 1.5 per cent volatile material may be expected to remain stable for three years when stored at a temperature slightly less than 20 C. Preliminary experience indicated that manufacturers should have no difficulty in keeping the moisture content of their product below 1.5 per cent.

As a complement to the laboratory studies, Stephenson, Probey and Harrison⁶⁶ investigated the relation of the age of neoarsphenamine to clinical reactions. In a five year period (1933 to 1937) the total number of injections of neoarsphenamine administered in the United States Navy was "541,381, representing 326 lots of three different manufacturers." The age of each lot of the drug was determined from the records of the National Institute of Health and was correlated with the incidence of reactions. The investigation showed that

the reaction expectancy increases as the age of the material increases [Neoarsphenamine] with an average age not in excess of 3 years shows a reaction

63 Training Opportunities in Syphilis Control, Announcements, Am J Syph, Gonorr & Ven Dis **22** 244 (March) 1938

64 Turner, T. B. The Qualifications of a Venereal Disease Control Officer, Am J Syph, Gonorr & Ven Dis **22** 269 (May) 1938

65 Harrison, W. T., and Probey, T. F. The Effect of Moisture and Age on the Stability of Neoarsphenamine, Pub Health Rep **53** 939 (June 10) 1938

66 Stephenson, C. S., Probey, T. F., and Harrison, W. T. The Effect of the Age of Neoarsphenamine on Reaction Expectancy, Pub Health Rep **53** 945 (June 10) 1938

expectancy of 1 to 1,312 doses as compared with the ratio of 1 in 870 doses in material older than 3 years, an increase of approximately 65 per cent

Kraft, Harris, Robinson and Gilliland⁶⁷ made quantitative studies of the arsenic distribution and excretion after intravenous injections of neoarsphenamine into 65 normal rabbits. They found, as have all other investigators, that "the organ predominantly concerned in the immediate removal of arsenic from the blood stream and its excretion is the liver. The intestines and kidneys follow in order." Their results also indicated that greater quantities of arsenic can be excreted in the urine than in the feces, although frequently this does not occur.

The Action of the Arsphenamines in Vitro—The earlier studies⁶⁸ on the mechanism of the action of the arsphenamines have led to the general belief that their therapeutic effect depends on conversion in vivo to another actively spirocheticidal substance. In a preliminary note, however, Eagle and Mendelsohn⁶⁹ report that arsphenamine, neoarsphenamine, silver arsphenamine and arsenoxide cause complete immobilization in vitro of virulent *S. pallida* obtained from rabbit testicular syphilomas. These immobilized organisms proved to be noninfectious for rabbits. Neoarsphenamine and arsphenamine had a definite spirocheticidal effect in vitro within eight hours in dilutions of at least 1 to 250,000, while arsenoxide immobilized the organisms in dilutions of 1 to 1,000,000. These concentrations, the authors point out, are of the same order of magnitude as those attained therapeutically. Further studies on this important subject are in progress, with particular reference to the influence of collateral factors.

Massive Dose Method of Treatment—Tzanck and his collaborators⁷⁰ are practicing a massive dose method which depends on the administration of 1.5 Gm. of neoarsphenamine on each of three successive days. The patients are hospitalized, and each injection requires three to five hours, as the solution flows drop by drop. In the majority of cases the immediate reaction is mild. In the treatment of 170 patients by this

67 Kraft, R. M., Harris, S., Robinson, C. S., and Gilliland, H. Quantitative Studies on Arsenic Distribution and Excretion After Intravenous Injections of Neoarsphenamine, *Am J Syph, Gonorr & Ven Dis* **22** 215 (March) 1938.

68 Ehrlich, P., and Hata, S. The Experimental Chemotherapy of Spirillosis, New York, Rebman Company, 1911. Voegtlin, C. The Pharmacology of Arsphenamine (Salvarsan) and Related Arsenicals, *Physiol Rev* **5** 63 (Jan.) 1925.

69 Eagle, H., and Mendelsohn, W. The Spirocheticidal Action of the Arsphenamines on *Spirocheta Pallida* in Vitro, *Science* **87** 194 (Feb. 25) 1938.

70 Tzanck, A., Duperrat, R., and Lewi, S. Arsénotherapie massive intraveineuse par instillation goutte à goutte, *Bull Soc franç de dermat et syph* **44** 2028 (Dec.) 1937, Traitement massif de la syphilis chez une malade qui avait été intolérante au novar 14 ans avant, *ibid* **45** 100 (Jan.) 1938, La médication arsenicale massive, *ibid* **45** 404 (March) 1938.

method there has been 1 case of polyneuritis but no other serious reaction. The rate of healing of visible lesions was remarkable.

Combined Fever and Chemotherapy—In continuing the search for means to shorten and to simplify the treatment of patients with early syphilis, Simpson and Kendell⁷¹ report the results of treatment of 34 patients by a combination of mechanically induced fever and chemotherapy. The patients usually were treated with ten five hour sessions, with the temperature held between 105 and 106 F and thirty injections either of 0.2 Gm of bismarsen or of 0.3 Gm of neoarsphenamine and a bismuth compound. At the time of the report the patients had been followed from one to four years after treatment had been completed, with no relapse observed. In contrast, relapse occurred in 2 of 6 patients who had received only the same amount of fever, and in 4 of 15 patients who had been given only the same amount of chemotherapy. The authors conclude:

While there exists no longer any valid reason to doubt the efficacy of artificial fever therapy in the treatment of neurosyphilis, the application of artificial fever therapy combined with chemotherapy to the treatment of early syphilis should be regarded as a strictly experimental undertaking for the next several years. It is obvious that the combined fever-chemotherapy method is not applicable at the present stage of its development to any mass management of the million or more individuals in this country who urgently require adequate treatment for syphilis each year. The standard schema of continuous chemotherapy proposed by the Cooperative Clinical Group of the U. S. Public Health Service provides the logical method for a mass attack upon the enormous number of cases of early syphilis which occur each year.

There is, however, urgent need for vigorous investigation of the possibility of reducing the time, inconvenience, and expense which characterize the present-day methods of treatment. Furthermore, there is evidence that the majority of patients now receive inadequate therapy and that inefficient chemotherapy interferes with natural reactive and curative forces.

The experimental treatment of early syphilis in 34 patients with artificial fever combined with chemotherapy appears to indicate that artificial fever intensifies the curative action of chemotherapeutic agents. There is evidence that the time required for adequate treatment of most cases of early syphilis can be greatly reduced. There is also evidence which indicates that smaller doses of chemical therapy administered over a shorter period exert an equal or greater curative action when combined with fever therapy than larger quantities of chemotherapy alone given over longer periods.

Fever therapy alone or chemotherapy alone, as applied to the control groups of patients in this study, was inadequate in a high proportion of cases. In certain instances in which syphilitic lesions progressed in spite of chemotherapy, these lesions began to heal promptly after instituting fever therapy.

The Kahn quantitative serologic procedure, as distinguished from the standard diagnostic test, appears to provide a sensitive and reliable guide to therapeutic

⁷¹ Simpson, W. M., and Kendell, H. W. Experimental Treatment of Early Syphilis with Artificial Fever Combined with Chemotherapy, *Am J Syph, Gonorr & Ven Dis* 21:526 (Sept) 1937.

response. Such quantitative measurements of the relative potency of the serum and spinal fluid of syphilitic persons provide the physician with an indication of the need for more treatment or for a different kind of treatment.

The response of certain patients who received a relatively short course of fever therapy, combined with chemotherapy, suggests that an equally favorable outcome might result from a shorter course of fever therapy in those patients who exhibit a prompt and uniform decline in the serologic reactions as measured by truly quantitative tests. Conversely, it is quite apparent that certain patients will require larger amounts of fever therapy or chemotherapy, or both. The urgent problem is to determine the minimum amount of effective fever therapy, combined with the minimum amount of chemotherapy, which will assure clinical and serologic cure, with full recognition of the probability that there will be occasional cases in which such minimum quantities will not be adequate. It is in this latter group of refractory cases that some quantitative serologic guide, such as the Kahn quantitative reaction, appears to be of indispensable value.

The constant development of simpler and safer methods for the production of artificial fever should stimulate vigorous inquiry of the possibility that the time, effort, and expense involved in the adequate therapy of early syphilis may be greatly lessened. Such studies should be restricted to those large clinics in which adequately trained personnel may engage in long-term, controlled experiments.

Mapharsen—Mapharsen continues to receive much favorable attention in the literature. Evidence has now accumulated to indicate that it is probably equal or superior to neoarsphenamine in therapeutic effect and that it produces fewer reactions than any of the arsphenamine products. The practically complete absence of nitritoid reactions and blood dyscrasias after its use and the low incidence of post-treatment dermatitis or jaundice are especially remarkable.

Cole and Palmer,⁷² Marshall⁷³ and Schmidt and Taylor⁷⁴ report on carefully studied groups of patients with various types of syphilis who were treated with mapharsen. These authors are in extraordinary unanimity in confirming the previous reports¹ regarding the efficacy of this drug.

From a discussion of their experiences with mapharsen in the treatment of patients with latent syphilis, Astrachan and Wise⁷⁵ conclude

The main objectives of the therapy of late latent syphilis may be obtained with equally good effects by mapharsen and neoarsphenamine. Mapharsen, however, being a drug of relatively lower toxicity, is preferable in late latent syphilis to other drugs possessing a greater tendency to produce untoward reactions.

72 Cole, H. N., and Palmer, R. B. Mapharsen in the Treatment of Syphilis, *Arch. Dermat. & Syph.* **36** 561 (Sept.) 1937.

73 Marshall, J. W. The Treatment of Syphilis with Mapharsen, *Am. J. Syph., Gonorr. & Ven. Dis.* **21** 645 (Nov.) 1937.

74 Schmidt, L. E., and Taylor, G. G. The Treatment of Syphilis with Mapharsen, *Am. J. Syph., Gonorr. & Ven. Dis.* **21** 402 (July) 1937.

75 Astrachan, G. D., and Wise, F. Further Experiences with Mapharsen. Its Use in Latent Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **22** 470 (July) 1938.

Chargin and Leifer⁷⁶ treated with mapharsen 50 syphilitic patients who showed seroresistance and found the drug neither more nor less effective than the other arsenicals in influencing the serologic reaction

Morgan⁷⁷ on the basis of his experience, concludes that in the treatment of congenital syphilis, mapharsen is the most powerful agent in effecting serologic "cure"

Jordan and Traenkle⁷⁸ report a study of 110 patients, who had previously reacted unfavorably to the arsphenamines, to whom they gave mapharsen. Most of the patients who had had gastrointestinal reactions after the administration of the arsphenamines tolerated mapharsen well. Of 20 patients who had had severe nitritoid reactions to an arsphenamine, not one had the reaction after an injection of mapharsen. Eighteen patients who had had postarsphenamine jaundice also were treated, and 16 tolerated the treatment well. In the other 2 patients jaundice recurred after the third and twelfth injections, respectively, of mapharsen. Two patients who had previously suffered from mild papular postarsphenamine dermatitis, tolerated an average of seventeen injections of mapharsen without recurrence of the dermatitis, and another, who had had a plaque-like arsphenamine dermatitis, was able to take eight injections of mapharsen, each of 0.03 Gm. Of 2 patients who had had urticaria after treatment with arsphenamine, 1 had urticaria after an injection of 0.01 Gm of mapharsen and the other showed no untoward effect after fourteen injections of 0.04 Gm. A recurrence of a previous fixed eruption due to arsphenamine developed in 1 patient after two injections of 0.03 Gm of mapharsen, and in another a mild recurrence of a crustaceous arsphenamine dermatitis appeared after the second injection of 0.01 Gm of mapharsen.

Bismuth—Wright⁷⁹ reports the results shown by 6 patients with early syphilis who from necessity were treated with bismuth alone for eighteen months to two years. Clinical and serologic "cure" resulted, and no relapse has occurred.

• 76 Chargin, L., and Leifer, W. Mapharsen in Wassermann-Fast Syphilis, *Am J Syph, Gonorr & Ven Dis* **22** 355 (May) 1938

77 Morgan, E. A. The Value of Mapharsen in the Treatment of Congenital Syphilis, *Canad M A J* **38** 52 (Jan) 1938

78 Jordan, J. W., and Traenkle, H. L. Reactions to Mapharsen, with Special Reference to Its Use in Patients Who React to the Arsphenamines, *Arch Dermat & Syph* **36** 1158 (Dec) 1937

79 Wright, C. S. Bismuth in Early Syphilis. Results in Seven Cases in Which Sole Reliance Was Placed on This Drug, *J Chemotherapy* **15** 1 (April) 1938

Waugh and Heering⁸⁰ found that thio-bismol (sodium bismuth thioglycollate) injected subcutaneously is satisfactory for clinical use in the treatment of patients with syphilis. They conclude, therefore, that it may be given to seamen for self administration while at sea.

Castallo and Rakoff⁸¹ treated 34 pregnant syphilitic women solely with weekly injections of 2 cc of a 10 per cent solution of quinine iodobismuthate (a red precipitate suspended in oil, with a bismuth content of 23.85 per cent). Twenty-six of the group were discharged with living, apparently healthy children, but 6 babies were stillborn, 1 died neonatally and 1 lived to show infection with syphilis. This clearly establishes the inefficacy of quinine iodobismuthate in the doses employed for the treatment of syphilis during pregnancy. It seems obvious, however, that the study constitutes a type of unnecessary and unjustified human experimentation which is to be condemned.

For the sake of uniformity Reindollar⁸² suggests the following specifications for bismuth subsalicylate, which pharmaceutical manufacturers would do well to adopt.

The Compound—Bismuth subsalicylate in oil contains 10 gm of finely ground U S P bismuth subsalicylate in sufficient peanut oil to make 100 cc. It meets the official requirements for purity, quality, and sterility adopted by the *National Formulary VI* for ampules of bismuth subsalicylate.

The Label—The label shall bear a statement of the kind of oil used. The concentration of bismuth salt shall be expressed as the quantity of bismuth subsalicylate, in grams, in 1 cc of suspension.

Iodobismutol—Barnett and Kulchar⁸³ studied the records of 827 patients with various forms of late syphilis who had been treated with iodobismutol with saligenin, usually with alternate courses of an arsenical. The results were completely satisfactory.

Hanzlik⁸⁴ presents new evidence of penetration of the cerebrospinal fluid by bismuth after treatment with iodobismutol with saligenin. The concentrations of bismuth were found to be variable, somewhat higher than previously reported and unrelated to the total dose of the drug, to other treatment or to the stage of the disease.

80 Waugh, J. R., and Heering, E. R. Subcutaneous Self-Administration of Bismuth for Selected Syphilitic Patients, *Hosp. News* 5: 27 (April) 1938.

81 Castallo, M. A., and Rakoff, A. E. Quinine Iodobismuthate in the Treatment of Syphilis Complicating Pregnancy, *Am. J. Obst. & Gynec.* 35: 137 (Jan) 1938.

82 Reindollar, W. F. Suggested Specifications for Bismuth Subsalsalicylate in Oil, *Am. J. Syph., Gonorr. & Ven. Dis.* 21: 679 (Nov) 1937.

83 Barnett, C., and Kulchar, V. Iodobismutol in the Treatment of Syphilis, *J. A. M. A.* 109: 1715 (Nov 20) 1937.

84 Hanzlik, P. J. Bismuth in Cerebrospinal Fluid After Administration of Iodobismutol, *Arch. Dermat. & Syph.* 37: 1003 (June) 1938.

Oral Administration of Bismutate—Thomas⁸⁵ treated 12 patients (9 with secondary lesions, 2 with a mucocutaneous relapse and 1 with a primary lesion on the lip) with bismutate^{85a} by mouth and was unable to confirm the favorable reports of Mulzer and Seieffs⁸⁶ on the efficacy of this drug when administered orally. She concludes "The promotion and sale of oral bismuth preparations should be curbed until more convincing proof of their effectiveness is produced."

Sobisminol—Pursuant to a preliminary report⁸⁷ on sobisminol, Hanzlik, Lehman, Richardson and Van Winkel⁸⁸ now present data from animal experiments from twelve detailed observations of the excretion of 7 persons after the administration of various doses of sobisminol and from weekly determinations of the bismuth content of the urine of 70 patients who were regularly receiving the drug. The results obtained leave no doubt of a prompt and well sustained absorption of bismuth and indicate that the oral administration of sobisminol in daily doses of 1.2 to 1.8 Gm. bids fair to be a practical therapeutic measure.

Sollmann and his associates⁸⁹ found that the oral administration of similar doses of sobisminol daily for three weeks gave curves for urinary excretion closely resembling those found after the intramuscular injection of water-soluble and oil-soluble bismuth compounds. The oral administration of bismuth and potassium tartrate, of sodium bismuth tartrate and of glycerite of bismuth in the advised doses, however, resulted in the excretion of therapeutically insignificant quantities of bismuth in the urine.

85 Thomas, C. C. Clinical Evaluation of Oral Bismuth (Bismutate) Therapy in Early Infectious Syphilis in the Female, *Am J Syph, Gonorr & Ven Dis* **21** 513 (Sept.) 1937.

85a According to the manufacturer, the composition of bismutate is as follows: a complex aminoacid-bismuth salt of oxytricarballic acid (bismuth chloride, sodium citrate, glycerine and liver extract), 64.14 per cent, saccharinum album, 25.6 per cent, talc, 3.3 per cent, stearic acid, 0.65 per cent, oil of anise, 0.01 per cent, succus glycyrrhizae, 3.3 per cent. Each tablet contains 200 mg. of metallic bismuth.

86 Mulzer, F., and Seieffs, S. Die perorale Wismutbehandlung der Syphilis, *München med Wchnschr* **81** 1525 (Oct. 5) 1934.

87 Hanzlik, P. J., Lehman, A. J., and Richardson, A. P. Sodium Bismuthate Soluble, *Am J Syph, Gonorr & Ven Dis* **21** 1 (Jan.) 1937.

88 Hanzlik, P. J., Lehman, A. J., Richardson, A. P., and Van Winkel, W. Clinical Excretion of Bismuth After Oral Administration of Sobisminol, *Arch Dermat & Syph* **36** 708 (Oct.) 1937, Gastrointestinal Administration of Sobisminol. Absorption, Distribution and Excretion of Bismuth, *J Pharmacol & Exper Therap* **62**:54 (Jan.) 1938.

89 Sollmann, T., Cole, H. N., Henderson, K., Binkley, G. W., Connor, H., Cooper, G., Schwartz, W. F., Sullivan, M., and Love, W. R. Clinical Excretion of Bismuth. V. Excretion of Sobisminol and of Some Other Bismuth Preparations for Oral Administration, *Arch Dermat & Syph* **37**:993 (June) 1938.

Excretion of Bismuth—Sollmann and his co-workers⁹⁰ found that the urinary excretion of iodobismutol after intramuscular injection resembled that of other water-soluble bismuth compounds. The excretion of iodobismutol was distinctly more sustained, however, so that two injections a week sufficed to maintain the same level of excretion as that obtained with three injections a week of citrate or tartrate. With thio-bismol (sodium bismuth thioglycollate), on the other hand, intensive urinary excretion was of short duration, the peak being reached on the day of the injection, with a low level shown on the succeeding day. It is therefore especially suited for rapidly attaining a relatively high concentration of bismuth for a brief period.

In order to correlate their numerous clinical studies of excretion with data on direct absorption, Sollmann and Henderson⁹¹ compared a series of bismuth compounds by determining the unabsorbed bismuth to be found at the site (usually) forty-eight hours after intramuscular injection into dogs. The preparations of bismuth studied may be arranged in four groups in descending order with regard to absorption. The highest was noted for thio-bismol, which was completely absorbed in two hours, the other aqueous solutions fell in the second and third groups, the oil solutions in the second, third and fourth groups and the oil suspensions in the fourth group.

The observations of Tauber and Clarke⁹² indicate that experimental animals reach a point beyond which no more bismuth is deposited in the viscera, regardless of dosage or length of administration.

From a study of the distribution of bismuth in the viscera of animals to which the drug had been given in various doses, the Fishbacks⁹³ draw some important conclusions. They found that while the kidney contained the highest concentration of bismuth, the greatest quantity of the drug was in the liver. In both of these organs, however, the accumulated bismuth was stored in the epithelial cells and was on its way out of the body, the authors feel that it is unlikely that significant

90 Sollmann, T, Cole, H N, Henderson, K, Binkley, G W, Connor, W H, and Sullivan, M. Clinical Excretion of Bismuth. II. The Urinary Excretion of Bismuth After Clinical Intramuscular Injections of Sodium Iodobismuthite (Sodium Bismuth Iodide, Iodobismutol) and Sodium Bismuth Thioglycollate (Thiobismol), *Am J Syph, Gonorr & Ven Dis* **21** 480 (Sept) 1937, III Fecal and Total Excretion, *ibid* **21** 492 (Sept) 1937, IV Late Excretion of Bismuth After Cessation of Treatment, *ibid* **21** 506 (Sept) 1937.

91 Sollmann, T, and Henderson, K. Clinical Excretion of Bismuth. VI. The Bismuth Absorption from the Site of Injection in Dogs, *Am J Syph, Gonorr & Ven Dis* **22** 286 (May) 1938.

92 Tauber, E B, and Clarke, G E. Daily Peroral Administration of Soluble Bismuth to Experimental Animals, *J Invest Dermat* **1** 109 (March) 1938.

93 Fishback, H R, and Fishback, D. Experimental Studies on Long-Continued Administration of Bismuth, *J Lab & Clin Med* **23** 127 (Nov) 1937.

resorption can take place from these deposits. The bones, on the other hand, contained a much lower concentration of the metal, but they provide the major storehouse from which the metal can be remobilized. Hanzlik, Lehman, Richardson and Van Winkle⁹⁴ describe a rapid clinical method of estimating the bismuth content of urine.

Mercury—Sidlick and Strauss⁹⁵ pose the question, "Is mercury a specific for syphilis?" In a clinical experiment (for which there seems no justification) on 10 patients who had primary syphilis and who showed negative results of serologic tests, they gave dailyunctions of 4 Gm of 50 per cent mercury ointment. Treatment was controlled by careful daily observation and serologic tests every third day. Under this regimen all the patients showed a positive reaction to serologic tests of the blood and clinical evidence of secondary syphilis.

Other Drugs—Sodium Thiosulfate. Ayers and Anderson⁹⁶ add to the confusing reports of the use of sodium thiosulfate for the relief of arsenical reactions. They obtained arsenic determinations for the urine of 49 patients with various cutaneous diseases in whom arsenic was suspected of being an etiologic factor. The tests were made before and immediately after a single injection of 10 cc of a 10 per cent solution of sodium thiosulfate. Eighty per cent showed a tenfold to hundredfold increase in the arsenic content of the urine after the injection.

Sulfanilamide. Campbell⁹⁷ found that sulfanilamide, administered in sufficiently large doses to constitute a valid therapeutic test, had no effect on experimental syphilis in the rabbit.

Ruthenium, Thorium, Rubidium, Cesium, Beryllium, Magnesium, Boron, Silicon, Zirconium, Hafnium, Phosphorus, Sulfur, Fluorine, Bromine, Rhenium and Erbium. Jahnel⁹⁸ continues his investigations on the chemotherapeutic action of a wide variety of elements and their compounds. He found that compounds of ruthenium exerted a slight effect in trypanosomiasis but had no effect on experimental syphilis in the rabbit. Similar negative results in cases of experimental syphilis⁹⁹

94 Hanzlik, P. J., Lehman, A. J., Richardson, A. P., and Van Winkle, W. Rapid Method for Estimation of Bismuth in Urine, *Arch. Dermat. & Syph.* **36**: 725 (Oct.) 1937.

95 Sidlick, D. M., and Strauss, A. Is Mercury a Specific for Syphilis? Preliminary Report, *Am. J. Syph., Gonorr. & Ven. Dis.* **22**: 358 (May) 1938.

96 Ayers, S., Jr., and Anderson, N. P. Sodium Thiosulfate and the Elimination of Arsenic, *J. A. M. A.* **110**: 886 (March 19) 1938.

97 Campbell, A. D. Note on the Failure of Sulfanilamide to Affect Syphilis in the Rabbit, *Am. J. Syph., Gonorr. & Ven. Dis.* **21**: 524 (Sept.) 1937.

98 Jahnel, F. Prüfung der chemotherapeutischen Wirkung des Rutheniums bei der experimentellen Syphilis, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **91**: 312 (Oct. 15) 1937.

99 Jahnel, F. Besitzen Thoriumverbindungen eine Heilwirkung bei Syphilis? *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **92**: 86 (Jan.) 1938.

were obtained with thorium chloride, thorium nitrate and thorium sulfate and with compounds of rubidium, cesium, beryllium, magnesium, boron, yttrium, silicon, zirconium, hafnium, phosphorus, sulfur, fluorine, bromine, thallium and erbium¹⁰⁰

UNTOWARD EFFECTS OF TREATMENT

Arsphenamine Dermatitis—Epstein¹⁰¹ presents a discussion of post-arsphenamine exfoliative dermatitis which is based on a study of 59 patients who had suffered from this distressing complication. Thirty-one of the patients had been treated by a well established routine, for the 28 others, treatment had been rather highly individualized. Otherwise the groups were similar. From this study he concludes that arsphenamine dermatitis is largely a preventable complication of the treatment of syphilis and that its incidence might be reduced by the preparation of all patients with late syphilis by means of treatment with heavy metal before institution of treatment with the arsphenamines.

He found that the reaction is most likely to occur during the first course of treatment with arsphenamine, it is more frequent when the patients are receiving simultaneous arsenical and heavy metal therapy and it shows a mortality rate of approximately 18 per cent. It was clear that the patients who were treated by the established routine method did better than those who received highly individualized types of treatment.

The dermatitis which develops after the administration of a trivalent arsenical is usually group specific and does not extend to the pentavalent compounds of arsenic. Epstein,¹⁰² however, reports on 2 patients, who were known to be sensitive to members of the arsphenamine series, in whom mild recurrences of exfoliative dermatitis appeared after the intravenous injection of tryparsamide in 1 case and after the insertion of devegan (a proprietary preparation containing acetarsone) into the vagina in the other. The rarity of this situation is exemplified by the fact that Ellis,¹⁰³ reporting a case of tryparsamide dermatitis of his own and reviewing the 11 previously reported cases in the literature, does not mention a similar example.

100 Jahnke, F. Chemotherapeutische Prüfung einer Reihe von chemischen Elementen bei experimenteller Syphilis, die bei dieser Infektion noch nicht Versucht worden sind, *Ztschr f Immunitätsforsch u exper Therap* **93** 184 (June 11) 1938

101 Epstein, E. Postarsphenamine Exfoliative Dermatitis, *J A M A* **109** 117 (July 10) 1937

102 Epstein, E. Sensitivity to Both Trivalent and Pentavalent Arsenicals, *Arch Dermat & Syph* **36** 964 (Nov) 1937

103 Ellis, F. A. Tryparsamide Dermatitis, *Am J Syph, Gonorr & Ven Dis* **22** 336 (May) 1938

Treatment of Peripheral Neuritis with Vitamin B₁—Gallowitsch ¹⁰⁴ reports on a patient with severe and extensive peripheral polyneuritis who made a dramatic recovery after treatment with vitamin B₁. The polyneuritis was thought to be due to the administration of a compound which contained arsenic, but the etiologic relation was far from established.

Relation of Vitamin C to Arsenical Reactions—The possible relation of vitamin C deficiency to arsenical reactions is receiving an increasing amount of attention in the literature. Unfortunately the papers which have appeared so far are relatively unconvincing. The question has not yet been approached from the experimental standpoint, though it seems vital to determine in animals whether, if the combination of vitamin C and arsphenamine actually reduces the toxicity of the latter, it may not also concomitantly reduce its therapeutic efficiency. Dainow ¹⁰⁵ says that his patients with vitamin C deficiency showed signs of arsenical intolerance which increased in severity with increase in the degree of hypovitaminosis. Patients who showed no evidence of hypovitaminosis, however, bore the arsenic well. On this basis he concludes that ascorbic acid prevents the oxidation of arsphenamine in the tissues and therefore decreases its toxicity.

Cormia ¹⁰⁶ states the following conclusion:

Variations in the vitamin C content of the diet, ranging from 0.025 to 0.2 mg. of cevitamic acid per day, had little if any influence on the development of cutaneous hypersensitivity in guinea pigs. At the lower levels of vitamin C diets, death from scurvy was common. A low vitamin C diet resulted in more indolent and more severe reactions than was previously encountered in a series of normal guinea pigs.

Friend and Marquis ¹⁰⁷ found a low vitamin C content of the blood in 5 patients who showed signs of arsenical intoxication, such as dermatitis, hepatitis, jaundice and nitritoid reactions. They conclude that in the absence of reactions, arsenical preparations do not cause any definite lowering of the vitamin C content but that in patients who do react a low vitamin C content of the plasma is apparently a result of the reaction rather than a predisposing factor.

From experiments with rabbits, Versari ¹⁰⁸ suggests that the detoxicating action of the amino acids, liver extracts and aminoacetic acid

104 Gallowitsch, P. Betaxin (Vitamin B₁) bei Arsen-Polyneuritis, *Munchen med Wchnschr* **84** 1138 (July 16) 1937.

105 Dainow, I. Intolérance aux arsénobenzènes et vitamine C, *Presse méd* **45** 1670 (Nov 24) 1937.

106 Cormia, F. E. Experimental Arsphenamine Dermatitis. The Influence of Vitamin C in the Production of Arsphenamine Sensitiveness, *Canad M A J* **36** 392 (April) 1937.

107 Friend, D. G., and Marquis, H. H. Arsphenamine Sensitivity and Vitamin C, *Am J Syph, Gonorr & Ven Dis* **22** 239 (March) 1938.

108 Versari, A. Ricerche sperimentali sulla azione svenenatrice della glicocola per gli arsenobenzoli, *Riforma med* **53** 1443 (Oct 9) 1937.

on arsphenamines is probably due to a protective synthesis, aminoacetic acid reacting with the drug to form a harmless product, which is eliminated

Cerebral Disturbances Accompanying Erythema of the Ninth Day—Milian¹⁰⁹ discusses the differential diagnosis of serous apoplexy caused by arsenicals and the cerebral disturbances which accompany erythema of the ninth day. Serous apoplexy is a grave complication. Usually on the first day there is excruciating headache, and the next day epileptiform attacks occur, followed shortly by coma and death. The cerebrospinal fluid is rich in albumin but contains few or no lymphocytes. Cerebral disturbances accompanying erythema of the ninth day, however, are less serious. Symptoms usually appear the day after the eruption develops. There may be confusion, agitation, some delirium, hyperesthesia of the skin and twitching of the muscles. Recovery is the rule. The findings in the cerebrospinal fluid are characteristic. There are always albuminosis (the value for albumin varying from 0.7 to 1.5 Gm.) and lymphocytosis (the lymphocytes showing a percentage varying from 34 to 75).

Hepatic Injury from Arsphenamine—Soffer and his colleagues¹¹⁰ report studies of the electrolytes of the blood and urine of 11 dogs in which acute diffuse hepatic parenchymal damage had been produced by the intravenous injection of arsphenamine, the dose ranging from 40 to 80 mg. per kilogram of body weight. Nine of the dogs died and 2 recovered. The most striking changes which they discovered were hemoconcentration, hypochloremia, a decrease in the carbonate content of the blood and an increase in the contents of lactic acid and inorganic phosphorus compounds. In 3 of the 11 dogs severe hypoglycemia also developed.

The authors do not relate their findings to the treatment of patients suffering from postarsphenamine jaundice. It seems clear, however, that their experimental data provide a rationale for the treatment of such patients with intravenous injections of solutions of sodium chloride and dextrose which has long been done empirically.

Hemorrhagic Encephalitis—Russell¹¹¹ describes 3 examples of hemorrhagic encephalitis following arsphenamine medication, in which there also occurred nonhemorrhagic perivascular areas of necrosis and demyelination.

109 Milian, G. L'erytheme du 9^e jour avec encephalite, Bull. et mem. Soc. med. d'hop. de Paris **53** 1372 (Nov. 22) 1937.

110 Soffer, L. J., Dantes, D. A., and Sobotka, H. Electrolytes of Blood and Urine of Dogs with Acute Hepatic Injury Produced by Arsphenamine, Arch. Int. Med. **60** 509 (Sept.) 1937.

111 Russell, D. S. Changes in the Central Nervous System Following Arsphenamine Medication, J. Path. & Bact. **45** 357 (Sept.) 1937.

Tryparsamide and Atrophy of the Optic Nerve—Mayer¹¹² reports on a group of 155 patients with neurosyphilis who were treated with tryparsamide. Fifty-four of the group had been observed by an ophthalmologist for at least five years, and 10 of these were said to have atrophy of the optic nerve, although the basis for the diagnosis is not clear. Two patients became blind, and 4 others showed constriction of the visual fields. The author concludes:

It would seem fair to state that tryparsamide under proper control is less dangerous than at first considered, even if optic atrophy has already become apparent. Patients with optic atrophy due to syphilis should have the advantage of the use of tryparsamide when the drug is indicated.

Bismuth Dermatitis—Jordon and Walker¹¹³ report on 2 patients in whom severe exfoliative dermatitis developed after the administration of a bismuth compound. In one instance camphobismol (a solution in olive oil of a basic bismuth derivative of camphocarboxylic acid) had been used and in the other a suspension of bismuth subsalicylate in oil. Both patients previously had had exfoliative dermatitis after the administration of an arsphenamine. The authors felt, however, that an arsenic compound as the precipitator of the reactions apparently related to bismuth could be excluded. They conclude that sensitivity to an arsphenamine may predispose to or be accompanied by sensitivity to bismuth compounds.

Phosphatase Determinations as an Index of Hepatic Damage—From their studies Lamb and Blakely¹¹⁴ reach the following conclusion:

Syphilis *per se*, does not elevate the blood plasma phosphatase [but] long continued neoarsphenamine administration in therapeutic doses causes a slight elevation. Phosphatase determinations may be of value as a means of indicating early liver damage in cases under treatment with neoarsphenamine.

Effect of Cystine—From theoretic considerations, Jurist and Christiansen¹¹⁵ reasoned that the administration of cystine might serve to reduce the toxicity of the arsphenamines. Experimentally, however, the toxicity of neoarsphenamine for albino rats was not materially reduced by the oral administration of 1 Gm of cystine per kilogram of body weight on the day following the injection of 350 mg of neoars-

112 Mayer, L. Tryparsamide Therapy of Neurosyphilis and Atrophy of the Optic Nerve, *J A M A* **109** 1793 (Nov 27) 1937.

113 Jordon, J W, and Walker, H L. Dermatitis Due to Bismuth Compounds Associated with Cutaneous Sensitivity to Arsenobenzols, *New York State J Med* **38** 483 (April 1) 1938.

114 Lamb, C L, and Blakely, E. A Study of the Phosphatase Elevation in Neoarsphenamine Administration, *New England J Med* **217**.353 (Aug 26) 1937.

115 Jurist, A E, and Christiansen, W G. The Effect of Cystine on the Toxicity and Trypanocidal Activity of Neoarsphenamine, *J Am Pharm A* **26** 497 (June) 1937.

phenamine per kilogram On the other hand, when doses of 250 and 500 mg of cystine per kilogram of body weight were administered orally on the day following the injection of from 5 to 9 mg of neoarsphenamine per kilogram of body weight to albino rats with trypanosomiasis, the trypanocidal action of the arsenical was clearly reduced

THE PROPHYLAXIS OF SYPHILIS

Cautley, Beebe and Dickinson¹¹⁶ emphasize the usefulness of good rubber sheaths in prophylaxis of venereal disease However, they point out that unfortunately only about 5 per cent of the rubber sheaths now sold in the United States are fit for use and that present methods for the evaluation of condoms are inadequate They suggest that physicians should originate attempts to improve and control the quality of the mechanical prophylactic equipment that is manufactured In this connection it is a matter of interest that the Food and Drugs Administration of the United States Department of Agriculture has undertaken the supervision of venereal disease prophylactics This supervision will apply not only to chemical substances sold for prevention of venereal disease (e g, sanitubes of one or another make) but also to condoms¹¹⁷

Chemical Prophylaxis—Mahoney's¹¹⁸ results indicate that prophylaxis by means of soap and water followed by inunction with mercurous chloride has a sound scientific basis, provided the soap and water is used within the first hour after the initial exposure and the ointment is thoroughly rubbed in The importance of the time element was shown by ingenious studies A suspension of *S pallida* was deposited on the intact genital mucosa of male rabbits, and at successive intervals the animals were killed for histologic study One hour after exposure began the organisms occupied a more or less protected position in the crypts of the mucous membranes In two hours there was evidence of penetration of the deeper tissues, and in three hours the organism had penetrated to a depth that would preclude the direct influence of any agent applied to the surface

Chemotherapeutic Prophylaxis—Levaditi¹¹⁹ found that as long as a high enough bismuth content was maintained in experimental animals, syphilis was prevented When administration of bismuth was discontinued, however, the animals became susceptible as soon as the metal reserve fell below that required for protection

116 Cautley, R, Beebe, G W, and Dickinson, R Rubber Sheaths as Venereal Disease Prophylactics, *Am J M Sc* **195** 155 (Feb) 1938

117 Mechanical Prophylaxis, editorial, *Am J Syph, Gonorr & Ven Dis* **21** 705 (Nov) 1937

118 Syphilis Prophylaxis, Notes and Comments, *U S Nav M Bull* **36** 121 (Jan) 1938

119 Levaditi, C Metallo-prevention bismuthique de la syphilis, *Bull Soc path exot* **30** 849 (Nov 16) 1937

EARLY SYPHILIS

The Genesis of Neurosyphilis—The question of whether antisymphilitic treatment provokes nervous symptoms was considered by Stranberg¹²⁰ in a study of 461 patients with late neurosyphilis. These he divided into four groups, as follows (1) patients who had received no treatment, (2) those treated only for late syphilis, (3) those inadequately treated for early syphilis and (4) those well treated from the beginning of the disease.

There were 257 patients (55.75 per cent) in groups 1 and 2, 185 patients (40.13 per cent) in group 3 and only 19 patients (4.12 per cent) in group 4. To the author these data indicated that vigorous antisymphilitic treatment had not provoked involvement of the nervous system but, on the contrary, had prevented it in this group of patients. This is in line with the present consensus, but one would need to know the percentage distribution into the four groups of the population from which these patients were drawn before accepting the author's conclusions.

In a monumental contribution Lomholt¹²¹ analyzes in detail the course of changes in the cerebrospinal fluid of patients with syphilis. The first portion of the monograph deals with the results of a total of 2,704 examinations of the cerebrospinal fluid of 2,399 patients. There were 1,521 patients with early syphilis, 257 of them were subjected to a second examination of the cerebrospinal fluid within a month after the institution of treatment. In addition, there were 155 patients with various forms of late syphilis, and 723 patients with clinically latent infections. For 48 of the latter group also repuncture was carried out within a month after the beginning of treatment.

Study of the various groups revealed that changes in the cerebrospinal fluid of untreated patients with primary syphilis were usually slight and relatively infrequent. In the cerebrospinal fluid of patients with primary syphilis who had received treatment, however, the changes were more frequent and more pronounced. The difference, Lomholt feels, is not due to the treatment but results from the longer duration of the infection in the latter group.

Changes in the cerebrospinal fluid of patients with secondary syphilis occurred more frequently and were more marked than those in the cerebrospinal fluid of patients with primary syphilis. The most pronounced changes were seen in patients with syphilis of longer duration.

¹²⁰ Stranberg, J. Investigation on the Prognosis of Syphilis with Especial Reference to Recidivation in the Brain and Marrow, Brit J Ven Dis 13:177 (July) 1937.

¹²¹ Lomholt, E. Course of Changes in the Spinal Fluid of Syphilitics, Copenhagen, Levin & Munksgaard, 1936.

duration and in those who suffered a relapse after previous treatment. In the absence of clinical relapse, however, changes in the cerebrospinal fluid of patients with secondary syphilis occurred with the same frequency and intensity whether or not they had received treatment.

In these groups, pleocytosis was the most commonly observed abnormality, with an increase in the protein content second in frequency. A positive reaction to the complement fixation test of the cerebrospinal fluid of patients with early syphilis was rarely observed.

Studies of the cerebrospinal fluid of patients with late or clinically latent infection revealed that abnormalities not infrequently occurred. There were, however, no conclusions to be drawn.

In the second portion of the monograph, data of crucial importance are presented. Of the 1,521 patients who had had one or more examinations of the cerebrospinal fluid early in the course of their infection with syphilis, 147 underwent repuncture one to thirteen years after the institution of treatment. The reexaminations revealed that (especially minor) abnormalities of the cerebrospinal fluid which are detected early in the course of the disease may disappear. For those patients whose cerebrospinal fluid on second examination revealed abnormalities, however, the first examination also had revealed abnormalities, provided it had not been made too early in the course of the infection. The late development of neurosyphilis was not observed among patients with clinically latent syphilis and normal spinal fluid. The author points out the value of the central index of the State Serum Institute of Denmark, where every syphilitic person is registered, thus making possible a study of this kind.

Clinical Phenomena in Early Syphilis—Skeletal Manifestations. Although osseous lesions are a common phenomenon in cases of late syphilis and many patients with early syphilis complain of pains in the bones and joints, syphilitic lesions are rarely demonstrable in the bones of patients with early syphilis. The case reported by Newman and Saunders¹²² is therefore of great interest. Their patient was a woman 28 years of age who complained of excruciating pain in all her extremities. Examination revealed a nondescript cutaneous eruption and a shallow ulcer on the tongue. Roentgenologic examination disclosed multiple areas of bony destruction involving the outer table of the frontal bone of the skull, the cortex of the right radius, both ulnas, the neck of the left humerus and both tibiae. The serologic test for syphilis gave a positive reaction, and on the basis of the ensemble a diagnosis of secondary syphilis was made. She improved dramatically with antisiphilitic treatment.

122 Newman, B. A., and Saunders, H. C. Skeletal System Manifestations During Secondary Syphilis, *New York State J. Med.* **38**: 788 (May 15) 1938.

Syphilitic Epididymitis According to McLachlan,¹²³ syphilitic epididymitis is more common than the number of published reports indicates. The diagnosis depends on the exclusion of other causes, the presence of serologic or other clinical evidence of syphilis, the demonstration of *S. pallida* in the lesion, complete resolution under anti-syphilitic treatment and no clinical alteration of the testes during the period of observation. He presents reports of 7 such cases, 3 of which occurred in patients with early syphilis and 4 in patients late in the course of the disease.

Capillaroscopic Appearance of the Chancre Nicolas and Liberman¹²⁴ describe characteristic differences in the capillaroscopic appearance of chancroid and chancre. Chancres are paler, and the capillary loops show a vertical arrangement, whereas in chancroid the loops are horizontal to the planes of the skin. This accounts for the undermining in chancroid.

Treatment of Early Syphilis—Sézary and Gallerand¹²⁵ point out that since Ehrlich's dream of *therapia sterilisans* for syphilis, investigators have not ceased to search for the treatment which if instituted early in the course of the disease would be capable of effecting a cure within a brief period. From a total of about 12,000 patients these authors selected for study 37 who had been under observation for periods varying from ten to sixty-nine months. All had come under observation with early syphilis, and all had received no more than two courses of treatment, each of which consisted of a total of 6.5 to 7 Gm of neoarsphenamine administered in doses gradually increasing from 0.15 to 0.9 Gm at intervals of two to seven days and, simultaneously, eighteen intramuscular injections of an oil suspension of an insoluble bismuth salt. They found 9 patients to be clinically and serologically normal at intervals varying from fourteen months to five years and nine months after treatment was discontinued. All had received two of these courses of combined treatment with bismuth and neoarsphenamine at regular intervals, with a rest period of no more than a month between courses. The 11 patients who received only a single course of treatment and the 17 patients whose treatment was irregular did not, on the average, fare so well. The authors feel, therefore, that further observations of this combined method of treatment are desirable, as

123 McLachlan, A. E. W. Syphilitic Epididymitis, *Brit J Ven Dis* **14** 134 (April) 1938.

124 Nicolas, N. W., and Liberman, T. N. Appreciation comparative du tableau capillaroscopique de la manifestation primaire de la syphilis et du chancre mou, *Ann de dermat et syph* **8** 700 (Sept.) 1937.

125 Sezary, A., and Gallerand, L. Resultats eloignes du traitement d'attaque novarseno-bismuthique conjugué institué pendant quelques mois au debut de la syphilis et non consolide, *Bull Soc franç de dermat et syph* **45** 990 (June) 1938.

offering a possible means of shortening the duration of treatment for patients who come under observation with early syphilis

TRANSFUSION SYPHILIS

Klauder and Butterworth¹²⁶ present an interesting case of accidental transmission of syphilis by the intravenous injection of washed leukocytes in the treatment of agranulocytic angina

LATE SYPHILIS

In a discussion of how syphilis may be traced through common ailments, Cannon¹²⁷ presents a study of the records of 300 patients who appeared to be free from manifestations of syphilis and who gave no history of recent syphilitic infection. Many of the patients were admitted for ailments supposedly unrelated to syphilis. One hundred and sixty-eight of the group were unaware of their syphilitic infection. Ninety-six presented as their chief complaint some banal ailment encountered in general practice—gastrointestinal disorders, chronic disorders of the respiratory tract, urinary symptoms, gynecologic ailments and miscellaneous disorders.

Ranula and Syphilis—Tsuzuki¹²⁸ reports histologic studies of ranula and the surrounding salivary glands in 27 cases. In 20 of these the serologic test for syphilis gave a positive reaction, in 7 the reaction was negative. Histologic evidence of syphilis was noted in all the former group. By Levaditi's method spirochetes were observed around the small blood vessels, pieces of tissue from 9 of the patients were inoculated into 28 rabbits, with positive results in 3 instances.

Syphilis of the Anus and Rectum—In a critical review of venereal diseases of the anus and rectum, Ault¹²⁹ describes the manifestations of syphilis. He reiterates that stricture of the rectum is rarely caused by syphilis. There is no typical picture of syphilis revealed through the proctoscope.

Syphilis of the Liver—Schumacher¹³⁰ discusses the relation of syphilis to Laennec's cirrhosis of the liver on the basis of a study of the clinical and autopsy records of 1,977 consecutive cases. Cirrhosis of the liver was demonstrated in 74 instances. Of the 45 patients with

126 Klauder, J. V., and Butterworth, T. Accidental Transmission of Syphilis by Blood Transfusion, *Am J Syph, Gonorr & Ven Dis* **21** 653 (Nov.) 1937

127 Cannon, A. B. The Tracing of Syphilis Through Common Ailments, *J A M A* **109** 348 (July 31) 1937

128 Tsuzuki, M. Ranula and Syphilis, *Am J Surg* **37** 127 (July) 1937

129 Ault, G. W. Critical Review Venereal Diseases of the Anus and Rectum, *Am J Syph, Gonorr & Ven Dis* **21** 430 (July) 1937

130 Schumacher, G. A. Causative Factors in the Production of Laennec's Cirrhosis, with Special Reference to Syphilis, *Am J M Sc* **194** 693 (Nov.) 1937

diffuse cirrhosis (including the Hanot type), 29 per cent had presumptive evidence of syphilis, approximately one third were known to have used alcohol to excess and 11 per cent were alcoholic addicts with syphilis. In one control group of 45 patients of the same age and sex who did not have cirrhosis and who were studied at autopsy, 2 (4.4 per cent) had had syphilis, and 2 had used alcohol to excess. In no instance were the two factors combined. In the other control group, of 24 persons with syphilis who were studied at autopsy, diffuse cirrhosis was found in 3 cases (12.5 per cent). The author concludes, therefore, that "syphilis long continued in association with alcoholism, and perhaps alone, may cause diffuse cirrhosis of the liver."

Irgang¹³¹ presents a general discussion of the relation between syphilis, antisyphilitic treatment and the liver. It is particularly important, he feels, to estimate the hepatic function of patients who react unfavorably to the arsphenamines. Early detection of arsenical hepatitis is essential if severe grades of inflammation are to be avoided. Tests of hepatic function should be performed when symptoms of intolerance continue longer than forty-eight hours.

According to Waugh¹³² the diagnosis of acute benign syphilitic hepatitis must depend on the occurrence of jaundice in a patient with untreated early syphilis. The condition is usually entirely asymptomatic, but having been suspected, the diagnosis is clinched by the occurrence of a Herxheimer reaction on the institution of treatment and by prompt cure if treatment is continued. The author reports 3 cases in which he felt the diagnosis could be accepted as proved and a fourth in which it seemed likely. He concludes that there is no danger of a severe Herxheimer reaction in the treatment of patients with benign hepatitis of early syphilis, provided treatment is instituted with small doses of an arsphenamine preparation and the patient is carefully watched.

Leukoplakia—Among 16,802 war veterans Eichenlaub¹³³ found 327 cases (1.9 per cent) of leukoplakia buccalis. Syphilis was entirely excluded in over 80 per cent of the cases, so he concludes that syphilis is not an important etiologic factor in the causation of leukoplakia.

Juxta-Articular Nodules—The subcutaneous fibroid nodules which are seen in patients with rheumatic fever and rheumatoid arthritis and the juxta-articular nodules which occur in patients with late syphilis

131 Irgang, S. The Problem of Involvement of the Liver in Syphilis, *Arch Dermat & Syph* **36** 684 (Oct.) 1937

132 Waugh, J. R. Benign Hepatitis of Early Syphilis, *Arch Dermat & Syph* **36** 599 (Sept.) 1937

133 Eichenlaub, F. J. Leukoplakia Buccalis, *Arch Dermat & Syph* **37** 590 (April) 1938

have been the subjects of extensive comment. Superficially, they are similar, and in the past there has been little effort to differentiate between them. McEwen¹³⁴ remedies this deficiency with a report based on the comparative histologic examination of eleven rheumatic subcutaneous nodules, eight nodules from patients with rheumatoid arthritis and two syphilitic juxta-articular nodules. He states that the histologic appearance of the first two types of nodules was identical but that the syphilitic nodules differed, presenting the appearance which is characteristic of syphilitic lesions in general.

The Infectiousness of Semen—In an important paper Kemp¹³⁵ considers the question of the infectiousness of semen of patients with late syphilis. A review of previous studies showed that spirochetes have been demonstrated in the semen of patients with early syphilis at about the same frequency with which they have been found during this stage in other body fluids. He found little reason, however, for the belief that the semen of patients with late syphilis is infectious. Experimentally fifteen specimens of semen from 15 patients with syphilis of four or more years' duration failed to produce syphilis in rabbits. Six of the 15 patients were untreated. In the other cases treatment antedated the examination of the semen by at least four years.

CARDIOVASCULAR SYPHILIS

Aortitis—Wilson¹³⁶ studied the clinical histories of 194 patients¹³⁷ in whom autopsy had revealed syphilis of the aorta, in an effort to determine whether the symptoms depended on aortic disease per se or on other factors. All the 49 patients with aortic insufficiency, 24 of the 31 patients with thoracic aneurysm and 20 of the 21 patients with narrowing of the coronary ostia had had one or more symptoms of circulatory embarrassment. On the other hand, 59 of the 106 patients with uncomplicated syphilitic aortitis had had no symptoms. All but 1 of those who had had symptoms had suffered from some complicating disease which could adequately explain them. Wilson concludes, therefore, that uncomplicated syphilitic aortitis is an asymptomatic condition.

134 McEwen, C. Cytologic Studies on Rheumatic Fever. III. A Comparison of Cells of Subcutaneous Nodules from Patients with Rheumatic Fever, Rheumatoid Arthritis and Syphilis, *Arch Path* **25** 303 (March) 1938.

135 Kemp, J. E. The Infectiousness of Semen of Patients with Late Syphilis, *Am J Syph, Gonorr & Ven Dis* **22** 401 (July) 1938.

136 Wilson, R., Jr. Studies in Syphilitic Cardiovascular Disease. I. Uncomplicated Syphilitic Aortitis, an Asymptomatic Condition, *Am J M Sc* **194** 178 (Aug) 1937.

137 Thirteen patients had more than one complication and were considered under both headings.

Wile and Snow¹³⁸ also are impressed with the frequency with which cardiovascular syphilis is asymptomatic, but they bring out that this may be true for aortic regurgitation and aneurysm as well as for uncomplicated syphilitic aortitis. Of their 210 patients, 83 had uncomplicated syphilitic aortitis, 66 had aortic regurgitation and 61 had aortic aneurysm. Of the first group, 54 per cent were found to have no symptoms referable to the cardiovascular system, of the second and third groups, 18 per cent and 20 per cent, respectively, had no cardiovascular symptoms.

In a general discussion along this same vein, White and Wise¹³⁹ say

It is evident that the early diagnosis of cardiovascular syphilis is practically impossible, that advanced and often rapidly fatal aortic disease is present (as shown by aortic regurgitation or aneurysmal aortic dilatation) by the time it is possible in most cases to diagnose cardiovascular syphilis.

Aortic Insufficiency—In the first of two papers Blackford and Smith¹⁴⁰ present the clinical impressions of syphilitic aortic regurgitation in Negroes which they have obtained by analysis of the records of 225 patients and, in addition, by intensive personal study of over half of them. They set up criteria for the diagnosis of syphilitic aortic regurgitation and point out especially the variability of the clinical course and the consequent difficulty of determining the prognosis. They feel, however, that the sudden onset of heart failure, pain and respiratory distress without edema are ominous prognostic signs. Regarding the influence of treatment they are convinced that

adequate treatment of early syphilis will prevent the development of syphilitic aortic insufficiency. The immediate indiscriminate use of the arsenicals in patients with late syphilis is dangerous. Bismuth therapy, with constant supervision, digitalis, and other measures as needed, promotes clinical improvement and probably prolongs life.

In the second paper¹⁴¹ these authors analyze the electrocardiograms of 128 patients with syphilitic aortic regurgitation and give the following conclusions:

Correlation between the clinical course of 47 patients with syphilitic aortic insufficiency and the QRS complex of serial electrocardiograms was found in 68 per cent of this group. The degree of myocardial damage as portrayed by

138 Wile, U. J., and Snow, J. S. Occult Cardiovascular Syphilis, *Am J M Sc* **195** 240 (Feb.) 1938.

139 White, P. D., and Wise, N. B. The Early Diagnosis of Cardiovascular Syphilis, *New England J Med* **217** 988 (Dec. 16) 1937.

140 Blackford, L. M., and Smith, C. Syphilitic Aortic Insufficiency in Negroes. I. Clinical Studies, *Am J Syph, Gonorr & Ven Dis* **22** 146 (March) 1938.

141 Smith, C., and Blackford, L. Syphilitic Aortic Insufficiency in Negroes, *Am J Syph, Gonorr & Ven Dis* **22** 168 (March) 1938.

all positive electrocardiographic findings closely paralleled length of life in the majority. The electrocardiograms in a group with heart pain and a group without heart pain was disappointingly similar. There was no electrocardiographic evidence to suggest an increased frequency of coronary ostial involvement in the group with pain. Positive electrocardiographic findings occurred often in both groups.

In comparing the electrocardiograms of these 128 patients with those of a group of 900 with other types of heart disease, they found that defective intraventricular conduction, left axis deviation, low voltage of the T wave and deviations of the ST segment occurred significantly more often among the patients with syphilis. Auricular fibrillation was found more often in the control group.

Influence of Early Treatment on the Development of Cardiovascular Syphilis—Kemp and Cochems¹⁴² again point out that the adequate treatment of early syphilis completely protects the cardiovascular system. They present a study of 743 patients who had received varying amounts of treatment for early syphilis. Of 208 patients who were followed for ten years or longer after treatment ended, the incidence of cardiovascular syphilis was 27.6 per cent in those receiving little or no treatment for early syphilis, when some, but inadequate treatment had been given, it was 13.9 per cent, and in 114 patients who had received adequate treatment, no cardiovascular syphilis was observed.

NEUROSYPHILIS

Expectancy—From the records of the Rigshospital and the Kommunehospital, and the registration of syphilitic persons at the State Serum Institute of Denmark, Lomholt¹²¹ was able to determine by actuarial methods the expectancy of a patient with syphilis that dementia paralytica will develop. Proper treatment of early syphilis, he says, lowers the risk of eventual paralysis, but the risk is present from five to fifty years after the initial infection. All determining factors being disregarded the risk is negligible during the first five years, rises to the order of 2 per thousand during the next decade, rises again to the order of 4 per thousand during the interval from fifteen to nineteen years after the initial infection and thenceforth remains at about 3 per thousand.

Incidence Among Chinese—Pfister¹⁴³ says that the idea that neurosyphilis is uncommon among Chinese must be abandoned. Comparing his personal observations in the neurologic clinics in Heidelberg, Ger-

142 Kemp, J. E., and Cochems, K. D. Studies in Cardiovascular Syphilis. IV. The Influence of the Treatment of Early Syphilis upon the Incidence of Cardiovascular Syphilis, *Am J Syph, Gonorr & Ven Dis* **21** 625 (Nov.) 1937.

143 Pfister, M. O. Mental and Nervous Diseases Among the Chinese, *Chinese M J* **50** 1627 (Nov.) 1936.

many, and in Peiping, China, he found tabes dorsalis to be half again as common among Chinese as among Germans. Erb's spastic paraplegia was especially common in the East.

Peptic Ulcer in Patients with Neurosyphilis—Because in their experience patients with syphilis of the central nervous system frequently came under observation with symptoms of peptic ulcer, Parsons, Ewalt and Gaskill¹⁴⁴ studied the records of 200 patients with neurosyphilis, 200 patients with latent syphilis, 100 patients with tuberculosis and 100 patients with a variety of diseases. They found the incidence of peptic ulcer to be 10.5 per cent in the first group and 1 to 3 per cent in the control groups.

Argyll Robertson and Tonic or Myotonic Pupil—Kennedy and his collaborators¹⁴⁵ draw attention to Adie's syndrome, which consists of tonic reactions of one or both pupils and total or partial absence of the deep reflexes. It has been mistaken for tabes dorsalis. In cases of the complete form one or both pupils fail to react normally to light and give a tonic reaction on convergence, in addition, some deep tendon reflexes are absent. The incomplete form may consist of abnormal pupillary reactions alone, absence of tendon reflexes alone or a combination of the two.

The differential diagnosis between the Adie syndrome and the Argyll Robertson phenomenon is important. In both cases the reaction of the pupil to light apparently is absent, but in the former the pupil will dilate in a dark room and may slowly overcontract, only again to expand to normal when exposed to ordinary illumination. The Argyll Robertson pupil, however, truly does not react to light. In addition, the Adie pupil is frequently (80 per cent) unilateral and if so is larger than its mate, the reaction during accommodation is overactive and too long sustained and the response to mydriatics is normal. The Argyll Robertson pupil, in contrast, is almost always bilateral, there is miosis, the reaction during accommodation, while it may be overactive, is promptly relaxed, and there is poor response to mydriatic drugs.

Myerson and Thau¹⁴⁶ report that the reaction of the Argyll Robertson pupil to light may be restored partially by the instillation of a dilute solution of benzedrine sulfate or by repeated subcutaneous injections or oral ingestion of the drug. They observed that dilatation in the dark and constriction in the daylight were slow but were deliberate and certain.

144 Parsons, E. H., Ewalt, J. R., and Gaskill, R. C. Peptic Ulcers in Syphilis of the Central Nervous System, *J. A. M. A.* **110** 1991 (June 11) 1938.

145 Kennedy, F., Wortis, H., Reichard, J. D., and Fair, B. B. Adie's Syndrome. Report of Cases, *Arch. Ophthalmol.* **19** 68 (Jan.) 1938.

146 Myerson, A., and Thau, W. Human Autonomic Pharmacology. XI. Effect of Benzedrine Sulfate on Argyll-Robertson Pupil, *Arch. Neurol. & Psychiat.* **39** 780 (April) 1938.

after benzedrine was administered. This phenomenon, the reverse of the reaction of the normal eye, throws doubt on the theories of the central origin of the Argyll Robertson pupil and suggests that the lesion may be in the iris.

Involvement of the Olfactory System in Neurosyphilis—Because the frontal portion of the brain has been shown frequently to be involved in cases of neurosyphilis, Darrah¹⁴⁷ tested a group of 75 patients with various types of syphilis by Elsberg's method of olfactometry. One patient had anosmia, and 4 others had impairment of the sense of smell. He concludes, therefore, that the olfactory system is seldom damaged by syphilis to the point of loss of function.

Tabes Dorsalis—There has recently accumulated a respectable body of opinion which holds that tabes dorsalis is not a disease entity but is, instead, part of a syndrome which is seen most frequently in cases of neurosyphilis. In this connection the study by Davison and Kelman¹⁴⁸ is of interest. These authors report that 5 of 15 patients for whom a clinical diagnosis of tabes dorsalis had been made showed on post-mortem examination degeneration of both the posterior and the lateral columns of the spinal cord.

TREATMENT OF NEUROSYPHILIS

Choice of Method—In a review of the treatment of syphilis with artificial fever, Neymann¹⁴⁹ says that with malarial therapy about 43 per cent of the patients with neurosyphilis achieve a remission or are greatly improved, whereas electropyrexia has increased the total rate of improvement by 21 per cent. He attributes a death rate of 10 to 30 per cent to treatment with malaria, however, and continues:

Certainly, electropyrexia has decreased this death rate to such a degree that it is no longer a problem. Indeed, if electromagnetic induction, combined with an air-conditioned treatment cabinet for maintaining the fever, is used by experienced personnel, there is no death rate.

In contrast to Neymann's gross overstatement of the death rate for induced malaria, Fong¹⁵⁰ reports that the death rate for induced tertian or quartan malaria for 1,012 patients was only 3.35 per cent. Necropsy was performed in half the 34 fatal cases. Seven deaths were found to

147 Darrah, L. W. Sense of Smell of Patients with Neurosyphilis, Especially of Those with Dementia Paralytica, *Arch. Dermat. & Syph.* **36** 1181 (Dec.) 1937.

148 Davison, C., and Kelman, H. Combined System Disease in Tabes Dorsalis, *Arch. Neurol. & Psychiat.* **38** 43 (July) 1937.

149 Neymann, C. A. Critical Review. The Treatment of Syphilis with Artificial Fever, *Am. J. Syph., Gonorr. & Ven. Dis.* **22** 92 (Jan.) 1938.

150 Fong, T. C. C. A Study of the Mortality Rate and Complications Following Therapeutic Malaria, *South. M. J.* **30** 1084 (Nov.) 1937.

be due to myocardial failure, 8 to acute malaria, 1 to pulmonary thrombosis and 1 to tuberculous bronchopneumonia. Two of the deaths due to acute malaria were caused by rupture of the spleen.

Bessemans¹⁵¹ also reviews the various methods of producing fever in animals and in man and describes a special thermometer which is suitable for the measurement of temperatures in a high frequency field. With it he has measured the tissue temperature of experimental animals while they were under treatment. The spirochetes which are found in the early lesions of syphilis of rabbits and of human beings, he says, are "thermolabile in vivo in a definite temperature time interval," while the spirochetes "found in the lymph nodes of syphilitic rabbits are more virulent and thermoresistant. In the latter case the thermoresistance is so great that it surpasses that of the organism of man and animals." The paradoxical and unexplained benefit of treatment with diathermy, which occasionally occurs in rabbits, is therefore "a sign of the reaction of the animal organism as a whole."

Trautman and Stroupe¹⁵² and Williams¹⁵³ report satisfactory results with mechanically induced fever in the treatment of small groups of patients with neurosyphilis.

Typhoid H Antigen—In the hands of Kulchar and Anderson,¹⁵⁴ treatment of 38 patients with neurosyphilis with typhoid flagellar (H) antigen in divided doses resulted in symptomatic and serologic improvement which compared favorably with that obtained with other forms of fever therapy. They suggest that because of its safety, it is a satisfactory method to employ in the treatment of patients whose physical condition precludes the use of other forms of nonspecific therapy.

The Blanket Method—Epstein¹⁵⁵ describes a simple method of producing fever by means of an electric blanket and presents the results obtained in the treatment of 87 patients with various forms of neurosyphilis by means of combined drug and fever therapy.¹⁵⁶ The clinical

151 Bessemans, A. Experimental Contribution to the Study of Antisyphilitic Hyperthermy Produced by Physical Agents, *Am J Syph, Gonorr & Ven Dis* **22** 479 (July) 1938.

152 Trautman, J. A., and Stroupe, H. V. Artificial Fever in the Treatment of Asymptomatic Neurosyphilis, *Hosp News* **5** 10 (May 1) 1938.

153 Williams, R. H. Results of Pyretotherapy at the Vanderbilt University Hospital, *South M J* **30** 1080 (Nov) 1937.

154 Kulchar, G. V., and Anderson, L. E. Divided Doses of Typhoid H Antigen in the Treatment of Neurosyphilis, *Am J Syph, Gonorr & Ven Dis* **21** 413 (July) 1937.

155 Epstein, N. N. The Blanket Method of Inducing Artificial Fever, *Arch Phys Therapy* **18** 199 (April) 1937.

156 Epstein, N. N. Artificial Fever as an Adjunct in the Treatment of Neurosyphilis, *Arch Dermat & Syph* **37** 254 (Feb) 1938.

results were good, and the Wassermann reaction of the spinal fluid became negative or showed considerable improvement in 73.4 per cent of the cases. Because of its simplicity and its beneficial effects, which compare well with those obtained with more elaborate methods, the author feels that the blanket method of inducing artificial fever is worthy of extensive trial.

Ape Malaria—Ciuca and his collaborators¹⁵⁷ have employed *Plasmodium knowlesi*, the organism of spontaneous ape malaria, for the treatment of 216 patients with dementia paralytica. They established the fact that malarial infection can be transmitted from man to monkey and back to man. After twenty-seven passages from man to man, the infection was transferred once through the monkey (*Macacus rhesus*) and then back to man. The clinical course of the malaria was found to be irregular, with a tendency to spontaneous abortion of the infection, although occasionally it appeared dangerously invasive.

Sequelae of Treatment with Malaria—It has been repeatedly observed that after treatment with malaria, allergic gummatous lesions of syphilis may develop in patients with neurosyphilis. In the literature Pilcz¹⁵⁸ was able to find reports of 52 such cases. These he describes briefly, and he discusses at length the possible theoretic explanations for the phenomenon. He does not emphasize that in all his series of cases the phenomenon followed treatment with malaria and not fever produced by other means.

Shock Syndrome After Therapeutic Hyperpyrexia—Kopp and Solomon¹⁵⁹ present a report which is based on a study of 8 patients who had severe reactions while under treatment in the Kettering hyperthermia by the standard technic. They point out that such reactions have much in common with the syndrome of shock and describe the typical picture as follows:

The reactions occurred at temperatures of 106 F or above, the body temperature usually showing some further rise. The impending shock was ushered in by a sudden increase in the pulse rate, pallor or cyanosis of the skin, a continued or rapid rise in the body temperature, fluttering of the eyelids, twitchings of muscles of the face or extremities, vomiting or sudden quietness, suggesting coma in a patient who had previously complained bitterly of the heat. Readings of the blood pressure when obtained at this time showed low levels, and in three patients the radial pulse was either weak or absent. The pulse rate at the onset was usually

157 Ciuca, M., Tomescu, P., Badenski, G., Badenski, A., Ionescu, P., and Tertiteanu, M. Contribution à l'étude de la virulence du *Pl. knowlesi* chez l'homme. Caractères de la maladie et biologie du parasite, Arch roumaines de path exper et de microbiol **10** 5 (March) 1937.

158 Pilcz, A. Ueber Tertiarismus bei Paralytikern nach Malaria-, bzw Rekurrensbehandlung, Wien med Wchnschr **87** 577 (May 22) 1937.

159 Kopp, I., and Solomon, H. C. Shock Syndrome in Therapeutic Hyperpyrexia, Arch Int Med **60** 597 (Oct) 1937.

rapid, from 120 to 164 per minute, and in one patient it increased from 130 to 180. In six patients these initial symptoms were followed by clonic or tonic convulsive movements of the jaw, extremities or trunk, and in five of the latter group the rigidity, either localized or generalized, was so marked that it was difficult to differentiate it from the tonic state of a convulsive seizure or muscle rigors due to heat cramps. In one patient repeated tonic and clonic convulsive seizures occurred over a period of four hours and resembled closely those due to strychnine poisoning and tetanus, the seizures being initiated by the slightest stimulus, such as a flash of light, a touch on the body, a jarring of the bed or the closing of a door, and being accompanied with maniacal excitement. In all patients considerable hyperactivity, jactitation and maniacal excitement occurred, and it was necessary to restrain them.

Treatment of the condition depends on reduction of the body temperature, relief of the dehydration and appropriate measures to remedy alkalosis and hypochloremia.

On the basis of thirty-one detailed studies of the water balance of 25 patients who were treated by means of fever artificially induced by various means, Gibson and Kopp¹⁶⁰ conclude

Artificial fever produced by physical means is characterized by a large gross water loss by way of the skin and lungs [This] may be far more rapid than absorption from the intestinal tract or tissue spaces, resulting in reduction in blood volume. Water is lost most rapidly during the induction of fever. While individuals vary in their response there exists for each a blood volume level beyond which further reduction leads to peripheral vascular collapse.

The rate of gross water loss during maintenance [of the fever] is related to the difference in temperature between the patient's body and the environmental air and to the relative humidity [of the latter].

The rate of loss of tissue fluids is directly related to the rate of fluid intake, and tissue fluid loss at a rate exceeding 5 cc per hour per kgm involves the risk of serious collapse. The prevention of shock in artificial fever therapy [therefore] is dependent on the giving of fluids in amounts and by routes adequate for the maintenance of the blood volume and water balance.

Treatment of Atrophy of the Optic Nerve—Lehrfeld and Gross¹⁶¹ present a study of syphilitic atrophy of the optic nerve which included 522 patients with primary atrophy and 48 with secondary atrophy.

Of the group of patients who received no treatment, 74.9 per cent were blind in less than three years, and all were blind at the end of a five year period. Of the group of patients who received routine antisymphilitic treatment, 23.8 per cent were blind in less than three years, and all were blind at the end of eight years. Of the group of patients who received a

160 Gibson, J. G., II, and Kopp, I. Studies in the Physiology of Artificial Fever. I. Changes in the Blood Volume and Water Balance, *J. Clin. Investigation* **17** 219 (May) 1938.

161 Lehrfeld, L., and Gross, E. R. A Statistical Investigation of Luetic Optic Atrophy, *Am. J. Ophth.* **21** 435 (April) 1938.

special form of treatment, including fever therapy and subdural injections, 28 per cent were blind in less than three years, and all were blind at the end of eight years

Menagh¹⁶² treated with hyperpyrexia combined with chemotherapy 99 patients who had various forms of neurosyphilis. Fifty-four per cent showed improvement, which was best in those with early involvement and minimal changes in the tissues

Among these patients were 10 with primary atrophy of the optic nerve. In 3 patients in whom the process was old and stationary, no improvement occurred. Two patients in whom the atrophy developed while routine treatment was being given went on to blindness, in spite of twenty-five and one hundred and twenty hours, respectively, of fever. Another was lost to observation. In the remaining 4 patients, however, the progress of the atrophy was arrested, and improvement occurred. In a discussion of the pathogenesis of atrophy of the optic nerve and its relation to the prognosis in an individual case, the author, on purely theoretic grounds, arrives at the conclusion that the occurrence of changes in the cerebrospinal fluid such as are seen in dementia paralytica makes the prognosis grave.

Acetarsone—Paddle¹⁶³ employed acetarsone in the treatment of 29 mental defectives who were found to have syphilis. The majority received six or seven courses of nine weeks each during a period of slightly more than two years. Improvement in physical condition took place in 27 patients and improvement in mental condition in 23 patients. Dermatitis was frequent, and 1 patient 61 years of age died of aplastic anemia.

For fifteen years Sézary and Barbe¹⁶⁴ have treated patients with neurosyphilis with sodium acetarsone, usually in courses of twenty-one to twenty-five injections of 1 Gm. once or twice a week, separated by periods of rest. The most striking therapeutic effects were observed in patients who exhibited excitement and megalomania. Patients with mental deterioration did not respond well.

Cobra Venom—Rottmann¹⁶⁵ reports good results with the use of cobra venom in the treatment of sensory symptoms in 2 cases of tabes

162 Menagh, F. R. The Treatment of Syphilis with Hyperpyrexia, with Observations on the Prognosis of Optic Atrophy, *Am J Syph, Gonorr & Ven Dis* **21** 609 (Nov) 1937

163 Paddle, K. C. L. Acetarsol in the Treatment of Late Congenital Syphilis Amongst Mental Defectives, *J Ment Sc* **83** 372 (July) 1937

164 Sézary, A., and Barbé, A. Les résultats cliniques et biologiques tardifs du traitement de la paralysie générale par le stovarsol sodique, *Presse med* **45** 1483 (Oct 23) 1937

165 Rottmann, A. Zur Therapie der sensiblen Reizsymptome bei Tabes dorsalis durch Kobratoxin, *Klin Wchnschr* **16** 1051 (July 24) 1937

syphilis in 3,000 pregnant women. They are, in the main, those that are generally held, but he emphasizes several points. As to the choice between arsphenamine and neoarsphenamine, he believes it is better for the physician to use the one with which he is most familiar, mercury, he feels, is superior to bismuth. In evaluating the status of a child after birth, he does not share the opinion that the serologic test of the cord blood is valueless. He agrees that a negative result of this test is of little value in deciding that a baby does not have congenital syphilis. In his experience, however, it is rare for a baby whose cord blood gives a positive reaction to a serologic test for syphilis not to show other manifestations of congenital syphilis.

Placental Transmission of Arsenic—Studies by Underhill and Amatruda,¹⁷¹ Kraul and Bodnar¹⁷² and Eastman¹⁷³ have shown that arsphenamine and bismuth are retained in relatively large amounts by the human placenta, chiefly in the fetal portion, that the storage of the drugs is cumulative with successive injections, and that these drugs may be found in the fetal organs and blood after treatment of the mother. Eastman and Dippel¹⁷⁴ later reported that although arsenic can be found only in minute traces or not at all in the blood of the newly born infant whose mother has received arsphenamine treatment, it is present in relatively huge quantities in the meconium. This suggests that whatever the manner (probably not simple diffusion through the placenta) in which it is transmitted from mother to fetus, arsenic is metabolized by the fetus in the usual manner and is available for the treatment of an already established fetal infection.

In contrast, Vamos and Bohm¹⁷⁵ describe experiments in which pregnant animals were given arsphenamine, after which the organs and tissues of both mother and fetus were examined for arsenic. The element was found in the decidual vessels and in the intervillous spaces but not in the chorion or in the organs of the fetus. These findings they interpret to mean that, while the defensive forces of the mother are greatly increased by treatment, this is much less the case with the fetus. Its defense is only passive.

171 Underhill, F. F., and Amatruda, F. G. The Transmission of Arsenic from Mother to Fetus, *J. A. M. A.* **81** 2009 (Dec. 15) 1923.

172 Kraul, L., and Bodnar, L. Ueber die Wirkung der antiluetischen Behandlung auf den Fetus, *Arch. f. Gynak.* **128** 238, 1926.

173 Eastman, N. J. The Arsenic Content of the Human Placenta Following Arsphenamine Therapy, *Am. J. Obst. & Gynec.* **21** 60 (Jan.) 1931.

174 Eastman, N. J., and Dippel, A. L. The Passage of Arsenic Through the Placenta Following Arsphenamine Therapy, *Bull. Johns Hopkins Hosp.* **53** 288 (Nov.) 1933.

175 Vamos, L., and Bohm, A. Die Wirkung der Arsenobenzolpraparate auf den Fetus, *Arch. f. Dermat. u. Syph.* **176** 245 (Dec. 8) 1937.

CONGENITAL SYPHILIS

Hoffman's Views—In a lecture on congenital syphilis Hoffmann¹⁷⁶ reiterates many of the generally accepted principles of the treatment of congenital syphilis, but the following views are not likely to remain unchallenged.

The objection was raised that instituting treatment among apparently healthy infants constituted a breach of the rule that there should be no treatment without a positive diagnosis. But in order to rule out congenital asymptomatic syphilis, a long period of observation, lasting from three to six months, is absolutely essential. Frequently, as a result of treatment instituted before birth, early diagnosis becomes impossible. As has already been said, it is of fundamental importance that treatment once begun should be continued until the maximum suitable dosage has been achieved. Furthermore, the less valuable time lost waiting, the quicker and easier is a complete cure obtained. Finally, apparently healthy infants withstand antisyphilitic treatment very well, and *it is no misfortune if a few really healthy children receive treatment along with the others*¹⁷⁷.

For all these reasons, it is preferable for infants of syphilitic mothers to receive preventive treatment, particularly since there is the danger that other members of the family will become infected. Unhappy experiences have induced me to go a step further in this direction and to recommend that the *wives of infected men receive a sufficiently energetic preventive treatment in order to avert familial syphilis for in this way the infection of the offspring is precluded*¹⁷⁷.

General Considerations—Cole¹⁷⁸ presents an excellent summary of modern concepts in regard to congenital syphilis. He prefers the use of the term prenatal to indicate that the infection has been contracted by the placental route. Whipple and Dunham¹⁷⁹ discuss the incidence, transmission and diagnosis of congenital syphilis. They quote the estimates that of 683,000 persons with syphilis who are constantly under observation in the United States, at least 60,000 are suffering from an infection transmitted by the parent. At present they believe that the generally accepted mode of transmission is from the syphilitic mother through the placenta, even though the mother may show no clinical manifestations of the disease. The diagnosis of congenital syphilis may be made only by a correlation of several factors: (1) demonstration of the disease in the parents, (2) examination of the placenta and cord, (3) pathologic examination of the stillborn infant, (4) clinical examination of the living infant, (5) serologic tests of the living infant and (6) roentgenologic examinations of the bones of the living infant.

176 Hoffmann, E. Congenital Syphilis, *Am J Syph, Gonorr & Ven Dis* **22** 198 (March) 1938.

177 The italics are ours.

178 Cole, H. N. Congenital and Prenatal Syphilis, *J A M A* **109** 530 (Aug 21) 1937.

179 Whipple, D. V., and Dunham, E. C. Congenital Syphilis. I. Incidence, Transmission and Diagnosis, *J Pediatr* **12** 386 (March) 1938.

In their second paper these authors¹⁸⁰ concern themselves largely with the debate as to whether the apparently normal child of a mother known to have syphilis should receive antisyphilitic treatment immediately after birth or only after the diagnosis of syphilis has been made with certainty. They say

The reasons that have been advanced for treating all infants born of syphilitic mothers are

- 1 It is often impossible to tell at birth which infants are infected with syphilis and which are not

- 2 Treatment of the mother results in treatment of the fetus in utero, and the infant at birth, although infected, may show no evidence of the disease. The treatment of the infant should not be interrupted at birth

- 3 In cases in which the mother is treated throughout pregnancy, a course of treatment given to the infant postnatally may be necessary to supplement his prenatal treatment

- 4 If a syphilitic infant, apparently healthy at birth, is not treated immediately after birth an unjustifiable risk is taken in that the disease may not be detected early and therefore treatment may be unnecessarily delayed

The reasons that have been advanced for withholding treatment until a definite diagnosis of congenital syphilis in the infant has been established are

- 1 If treatment for syphilis is begun it should be continued for a long time

- 2 It is impossible to evaluate the results of therapy unless the diagnosis is established in each instance

- 3 It is not justifiable to place the stigma of syphilis on a nonsyphilitic child

- 4 It is a needless risk to submit a nonsyphilitic infant to the hazards of anti-syphilitic therapy

- 5 It is an unjustifiable expense to treat nonsyphilitic infants

In their opinion, these differences in attitude are based largely on differences in interpretation of the mechanism of prenatal treatment of the mother, if such has occurred, and will not be resolved until fundamental investigation settles the question of treatment of infection of the fetus in utero

Diagnosis—In order that treatment of congenital syphilis may be begun at the earliest possible moment, an accurate method of diagnosis in the first few months of life, the so-called period of doubt, is of great importance. According to Faber and Black,¹⁸¹ the use of a quantitative rather than a qualitative technic for testing the blood of infants of syphilitic mothers offers a means of early differentiation between infants who have been infected with syphilis and those who have not. Chris-

180 Whipple, D. V., and Dunham, E. C. Congenital Syphilis. II. Prevention and Treatment, *J. Pediat.* **13** 101 (July) 1938

181 Faber, H. K., and Black, W. C. Quantitative Wassermann Tests in Diagnosis of Congenital Syphilis. Clinical Importance of Fildes Law, *Am. J. Dis. Child.* **51** 1257 (June) 1936

tie ¹⁸² presents evidence to support this view. His report is based on a study of 14 newborn infants of mothers with syphilis. The blood of these infants gave a positive reaction to a quantitative complement fixation reaction when first tested. None of these infants presented any clinical or roentgenologic evidence of syphilis, all were followed with repeated quantitative serologic tests, roentgen examinations and clinical observations for a minimum period of four months. In 11 of the infants the reagin titer progressively diminished, and eventually the reaction became and remained negative. In none of these did clinical or roentgenologic evidence of syphilis develop. In 3 children who were apparently normal at the time of the first serologic test, however, the initial decrease in reagin titer was followed by a sharp increase. All these infants subsequently showed clinical or roentgenographic evidences of congenital syphilis.

Higouménakis ¹⁸³ calls attention to enlargement of the sternal end of the clavicle (usually the right) as a sign that establishes the diagnosis of congenital syphilis. He says that the "sign of the clavicle" is superior in its diagnostic value to any of the other stigmas of congenital syphilis because of the regularity of its occurrence and the ease with which it may be detected. The ease of detection of this sign is obvious, the author does not document his assertions concerning its frequency.

Control—Ingraham ¹⁸⁴ says

Assuming a perfect medico-therapeutic approach to the problem of congenital syphilis control, three social and administrative difficulties still block our full accomplishment in this field. (1) Pregnant syphilitic women do not usually report for prenatal supervision until late in pregnancy, (2) a delay of some weeks between the initial ante-partum visit and the onset of antisymphilitic therapy is a common occurrence, (3) congenitally syphilitic offspring are frequently not treated in *early* infancy.

Identification of Spirochetes in the Placenta—Dorman and Sahyun ¹⁸⁵ revoice the common experience that a newborn baby may look healthy, the placenta may be normal grossly and the serologic test for syphilis of the cord blood may give a negative reaction, yet the child may have congenital syphilis. Even the histologic appearance of the placenta does not establish the diagnosis. Therefore, the identification of spirochetes in the placenta is important in the diagnosis of congenital

182 Christie, A. U. Diagnosis of Syphilis in New Born Infants. Use of Quantitative Wassermann Tests, *Am J Dis Child* 55 979 (May) 1938.

183 Higouménakis, G. C. Le signe de la clavicule et sa valeur diagnostique dans la syphilis héréditaire, *Ann de dermat et syph* 8 939 (Dec) 1937.

184 Ingraham, N. R. The Importance of Treatment in the Control of Congenital Syphilis, *Ven Dis Inform* 19-124 (May) 1938.

185 Dorman, H. G., and Sahyun, P. F. Identification of Spirochetes in the Placenta, *Am J Obst & Gynec* 33 954 (June) 1937.

syphilis In portions of the placenta which showed pale yellow foci surrounded by a dark granular periphery, they demonstrated spirochetes which could not be differentiated morphologically from *S. pallida* in 105 cases

Syphilitic Children of Untreated Mothers Who Gave a Negative Reaction to Serologic Tests—Waugh¹⁸⁶ reports on 2 women who showed a negative reaction to tests of the blood and cerebrospinal fluid for syphilis, who revealed on careful physical examination no evidence of syphilis and who had had no treatment for the disease There could be no doubt, however, that each had given birth to a child with prenatal syphilis

Interstitial Keratitis—Lazarescu's¹⁸⁷ discussion is based on an almost unique opportunity to study 349 patients with interstitial keratitis due to congenital syphilis Other stigmas of congenital syphilis were present in 269 (77 per cent) The process involved both eyes in 248 cases but had appeared simultaneously in only 80 In 81 per cent of the cases in which the time intervals were accurately known, however, the second eye had become involved within thirty days of the onset of the process in the first eye

The ages of the patients at the onset of interstitial keratitis varied from 1 year to more than 60 years, but the onset occurred between the ages of 6 and 15 years in more than half the cases Trauma seemed to play no part in initiating the process

The results of treatment were only mediocre, although the author seems well pleased The process became bilateral in 14 of the 101 patients for whom treatment was started while only one eye was involved

Familial Syphilis—In a recent communication from Switzerland it is said¹⁸⁸

Robert Rossle, pathologic anatomist of Berlin, then spoke on the familial behavior of tuberculosis and syphilis Necropsy records of married couples and blood relations were systematically assembled and collated with respect to the problem of familial behavior of the two most important diseases of the people Among the pertinent considerations is that of special organotropic strains and of the causative organisms and of organic predispositions to attack With respect to syphilitic married couples, the observation that the death of one spouse was usually followed after no great interval by that of the other led to the presumption of a similarity of agent The high incidence of congenital syphilis among siblings was regarded in the same light Yet, apart from rare exceptional instances, no

186 Waugh, J R Untreated Seronegative Mothers of Syphilitic Children, *J Pediat* **11** 490 (Oct) 1937

187 Lazarescu, D Faits resultant de 349 observations de keratite hérédo-syphilitique, *Arch d'opht* **53** 756 (Oct) 1936

188 International Medical Week, Foreign Letters (Switzerland), *J A M A* **109** 1827 (Nov 27) 1937

evidence of an identity in the disease was manifested among marriage partners or in congenital syphilis as observed among siblings. On the whole, familial syphilis presents the same variegated and chequered picture as extrafamilial syphilis.

From a study of 46 patients with juvenile dementia paralytica who were personally observed and of 610 patients reported on in the literature, Menninger and Grotjahn¹⁸⁹ were able to obtain definite information about the family history in 402 cases. In 146 of these cases (36 per cent) there was clinical evidence of neurosyphilis in one or more of the other members of the family. To quote the authors:

As stated at the beginning of this paper, our purpose has been to present further clinical evidence suggesting the existence of a neurotropic strain of *S. pallida*. We regard the theory of familial predisposition as a thinly cloaked disguise for an unclear concept and believe that the mass of clinical evidence suggests definitely that the micro-organism itself must in some instances have a specific affinity for, or at least a tendency to reside in and carry on its destructive work on, the nervous tissue.

The Treatment of Congenital Syphilis—Yampolsky¹⁹⁰ presents a comparative review of methods for the treatment of congenital syphilis and makes detailed suggestions for alternative methods of treatment. He voices a seemingly unnecessary warning against the use of tryparsamide:

We are already dealing with a constant possibility of the development of interstitial keratitis, and we certainly should bear in mind that the risk of blindness is too great in patients when this drug is used.

Smith, Fried and Everhart¹⁹¹ regard acetarsonsone as the drug of choice for the treatment of congenital syphilis during the first year of life and take exception to the statement of Cole,¹⁹² who said "As yet I am unwilling to recommend the indiscriminate use of acetarsonsone by mouth in the treatment of congenital syphilis. It is still too much in the experimental stage", and of Stokes,¹⁹³ who said "Acetarsonsone has by no means proved its place in the treatment of syphilis, although a decade has elapsed since its introduction." Smith and his co-workers believe that many of the severe toxic reactions reported are due to unnecessarily large doses, so they recommend a modification of the Bratusch-Marrain

189 Menninger, W. C., and Grotjahn, M. Familial Neurosyphilis of the Dementia Paralytica Type, *Arch Neurol & Psychiat* **39** 343 (Feb.) 1938.

190 Yampolsky, J. A Comparative Review of the Antiluetic Drugs in the Treatment of Congenital Syphilis in Children, *South M J* **31** 406 (April) 1938.

191 Smith, E. E., Fried, R. I., and Everhart, M. W. The Treatment of Congenital Syphilis with Acetarsonsone, *Ohio State M J* **34** 165 (Feb.) 1938.

192 Cole, H. N. The Pharmacopeia and the Physician. Use of Anti-syphilitic Remedies, *J A M A* **107** 2123 (Dec. 26) 1936.

193 Stokes, J. H. Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1934, pp. 345-346.

scale, beginning with a daily dose of 5 mg per kilogram of body weight. Treatment with mercury and chalk, they feel, is the most satisfactory to give between courses of acetarsone.

SERORESISTANCE

Moore and Padget¹⁹⁴ discuss the problem of seroresistance, or "Wassermann fastness." They define as seroresistant those patients with early syphilis for whom the reaction of the serologic test for syphilis remains positive after six months of continuous treatment and those with late syphilis (i.e., having been infected with syphilis for more than two years) for whom the serologic test continues to give a positive reaction after the equivalent of a year of treatment. In cases of early syphilis, seroresistance must be regarded as a manifestation of persistent foci of organisms or progressive activity; in cases of late syphilis, it may result from the persistence of well established immunity.

The type of infection at the beginning of treatment influences the development of seroresistance. Treatment during early syphilis has an important bearing on seroresistance. Eleven per cent of a group of patients who received continuous treatment were seroresistant, but 37 per cent of those treated intermittently and 68 per cent of those treated irregularly showed positive serologic reactions six months after treatment had started.

The presence or absence of involvement of the neuraxis in cases of early syphilis is also of importance in determining the incidence of seroresistance. The influence of other factors being disregarded, seroresistance is encountered in only a sixth of the patients whose cerebrospinal fluid is normal but occurs in almost half of those whose cerebrospinal fluid gives a positive complement fixation reaction.

In patients with late syphilis, however, the situation is different. The incidence of seroresistance is not influenced by the scheme of treatment employed, nor is it related to the existence of involvement of the neuraxis *per se*. Instead, it may be viewed as an integral part of the manifestations of many late forms of the disease.

The foregoing data concern patients who receive adequate anti-syphilitic therapy or, if the treatment is irregular or intermittent, those who receive adequate doses when treatment is given. There is no information which allows a clear evaluation of the effect of treatment with inadequate doses of drugs on the course of either early or late syphilis. From theoretic observations and deductions based on clinical observations, however, it seems probable that inadequate doses, even given according to a system of continuous treatment, are a potent factor in the production of seroresistance.

¹⁹⁴ Moore, J. E., and Padget, P. The Problem of Seroresistant Syphilis, (So-Called Wassermann Fastness), *J. A. M. A.* **110** 96 (Jan. 8) 1938.

The significance of seroresistance must be considered separately in early and in late syphilis. For example, of a group of patients with early syphilis who had received adequate treatment, 23 per cent of those who were seroresistant but only 5 per cent of those who manifested a prompt serologic reversal sustained infectious relapse, similarly, neurosyphilis occurred in 31 per cent of the former group but in only 18 per cent of the latter.

A contrasting situation obtains in cases of late syphilis. For each type of late syphilis considered, the incidence of progression or relapse is essentially the same in patients who are resistant as in those who are not, indeed, in the case of latent or benign late syphilis, relapse occurs somewhat more frequently in patients who are not seroresistant than in those who are. Progression or relapse developed in 4.6 per cent of patients with latent syphilis who were seroresistant and in 5.7 per cent of those who were not. In the case of benign late syphilis one of these eventualities developed in 9.8 per cent of the seroresistant patients and in 12.2 per cent of the patients who had experienced serologic reversal. Of the group with late congenital syphilis, 21.5 per cent of those who were seroresistant and 20 per cent of those who were not manifested progression of the disease later. In patients with these types of late syphilis, therefore, seroresistance may actually be beneficial rather than harmful.

In patients with other forms of late syphilis, especially cardiovascular syphilis or neurosyphilis, seroresistance is so common that the impossibility of placing special interpretation on its occurrence is readily apparent.

The rationale of the management of patients with seroresistance may be logically developed from a consideration of the aims of the treatment of syphilis, early or late. These are the healing of lesions and the relief of symptoms, the maintenance of good health and the prevention of progression or relapse, and, least important, serologic reversal. If the first and second aims can be accomplished, success or failure of the third should be a matter of complete indifference.

The following outline is provided for the management of the patient with seroresistance.

In Patients with Early Syphilis

I. Examine the cerebrospinal fluid

- A. If reaction is positive. Alter system of treatment to that for early asymptomatic neurosyphilis.
- B. If reaction is negative
 - 1. Eliminate rest periods—treatment must be continuous.
 - 2. Employ full dosage of a potent arsphenamine.
 - 3. Prolong treatment for a full year of weekly injections after serologic reversal is obtained.

In Patients with Late Syphilis

- I Examine the cerebrospinal fluid
- II Conduct a searching clinical study for lesions of syphilis, with particular reference to
 - A The cardiovascular system (including roentgenologic examination)
 - B The central nervous system
 - C The bones
- III If abnormalities in any of these systems are discovered, plan treatment accordingly
- IV If no abnormalities are discovered
 - A Prolong treatment to a minimum of two years, continuously and with full doses
 - B Follow the patient for the rest of his life, with, periodically, complete and searching resurveys of his clinical status
 - C Frankly discuss and fully explain the situation to the patient and give him as much reassurance as possible

Special Treatment of Seroresistant Patients—The length to which some feel it necessary to go to obtain serologic reversal in a patient who shows seroresistance is demonstrated by the report of von Hecht-Eleda and Riehl¹⁹⁵ These authors treated 37 patients with latent syphilis and 3 patients with late congenital syphilis by withdrawing 10 cc of blood, exposing it to ultraviolet radiation and reinjecting it intramuscularly In 27 per cent of the cases the seroreactions became negative Baer¹⁹⁶ also reports the treatment of 27 "Wassermann fast" patients by means of combined ultraviolet irradiation and autohemotherapy Gougerot and Durel¹⁹⁷ feel that treatment with induced fever is necessary in the management of patients who show seroresistance with the usual methods of therapy

The enormity of the crime against the patient which such maneuvers represent cannot be too strongly emphasized As just pointed out, seroresistance arises from a variety of causes and likewise has varied significance Under many circumstances it is meaningless and should be disregarded, in a few instances its import is ominous and should be

195 von Hecht-Eleda, M, and Riehl, G, Jr Zur unspezifischen Luestherapie Bericht uber die Reinjektion ultraviolett bestrahlten Eigenblutes nach Havlicek bei Therapieresistenter seropositiver Lues latens, Arch f Dermat u Syph **178** 8, 1937

196 Baer, H L Ultraviolet Irradiation and Autohemotherapy in Syphilis Treatment of Persistent Serologic Positive and Latent Syphilis, Pennsylvania M J **40** 943 (Aug) 1937

197 Gougerot, H, and Durel, P Pyretotherapie dans la syphilis cutanees, les Bordet-Wassermann irreductibles et la dermatologie, Ann d mal ven **32**. 241 (April) 1937

heeded In either event, however, the interpretation of seroresistance properly should be based on a careful evaluation of the ensemble and not on the mere fact that the laboratory report shows a positive reaction to a serologic test for syphilis

YAWS

Numerous investigators, including Noguchi and Mooie,¹⁹⁸ Wile,¹⁹⁹ Jahnel,²⁰⁰ Wilson²⁰¹ and Kopeloff and Blackman,²⁰² have demonstrated the presence of spirochetes in the cerebral cortex of patients with dementia paralytica, but often the parasites were present only in small numbers and in atypical forms Saunders,²⁰³ however, found great numbers of spirochetes in the brains of 5 of 9 Jamaicans brought to autopsy with a diagnosis of dementia paralytica Because of the prevalence of yaws, he considers the possibility that this disease may produce a type of dementia paralytica in which spirochetes are more abundant than in the syphilitic disease As he points out, however, in only 1 of the 5 cases had treatment for syphilis been given prior to death, in contrast to many of the cases reported by other authors in which the patients had been treated with malaria or arsenical drugs or both

From a study of biopsy specimens from comparable lesions of 38 patients with yaws and 14 patients with syphilis, Ferris and Turner²⁰⁴ conclude "Histologic criteria for the differentiation of the cutaneous and subcutaneous lesions of yaws and syphilis are in general unreliable"

Takahasi²⁰⁵ made comparative studies of the lesions produced in rabbits by the spirochetes of yaws and syphilis Grossly the syphilitic chancres were harder than the frambesic chancres Histologically, there

198 Noguchi, H, and Moore, J W A Demonstration of *Treponema Pallidum* in the Brain in Cases of General Paralysis, *J Exper Med* **17** 232, 1913

199 Wile, U J The Demonstration of the *Spirochaeta Pallida* in the Brain Substance of Living Paretics (Forster and Tomaszewski), *J A M A* **61** 866 (Sept 13) 1913, Experimental Syphilis in the Rabbit Produced by the Brain Substance of the Living Paretic, *J Exper Med* **23** 199, 1916

200 Jahnel, F Die Spirochäten im Zentralnervensystem bei der Paralyse, *Ztschr f d ges Neurol u Psychiat* **73** 310, 1921

201 Wilson, R B Histological Changes Following the Malarial Treatment of General Paralysis, *Brain* **51** 440 (Dec) 1928

202 Kopeloff, N, and Blackman, N Spirochetal Findings in the Brains of Paretics Treated with Malaria, *Am J Psychiat* **13** 21 (July) 1933

203 Saunders, G M Spirochete in the Brain in General Paresis in Jamaica, *Am J Syph, Gonorr & Ven Dis* **22** 503 (July) 1938

204 Ferris, H W, and Turner, T B Comparative Histology of Yaws and Syphilis in Jamaica, *Arch Path* **24** 703 (Dec) 1937

205 Takahasi, H Histopathologic Study of Experimental Syphilis and Frambesia in Rabbits II Orchitis and Primary Lesions of Skin and Back of Scrotum, *Jap J Exper Med* **15** 401 (Dec) 1937

were characteristic differences. *S. pallida* showed predilection for connective tissue and blood vessels and caused diffuse cell infiltration, whereas *T. pertenue* had no special affinity for connective tissue or blood vessels, and the infiltrations were localized.

INTERRELATION OF SYPHILIS AND OTHER DISEASES

Tuberculosis—During the past six and a half years Smith²⁰⁶ has treated 69 patients with tuberculosis for syphilis. From his results he concludes that progressive tuberculosis is no more frequent in treated syphilitic patients than in similar groups of nonsyphilitic tuberculous patients, that treatment of syphilis lessens the frequency of progressive tuberculosis and that adequate treatment of syphilis of tuberculous patients is justified.

In an investigation of great significance, Aronson and Meranze²⁰⁷ studied the lesions produced by the injection of tubercle bacilli into the skin of syphilitic and nonsyphilitic rabbits. The local inflammatory reaction was more intense in the syphilitic rabbits than in the similarly treated nonsyphilitic controls. Three hours after the infection and continuing throughout the period of observation the lesions in the syphilitic rabbits were multiple and focal and were distributed along the capillaries. In the nonsyphilitic rabbits the lesions were single and diffuse and bore no relation to the vascular distribution. Forty-eight hours and three weeks later the lesions excised from the syphilitic animals resembled histologically the primary and secondary lesions of syphilis. The authors conclude that the cellular response in syphilitic rabbits is what has been termed an *anamnestische* reaction, i.e., the cells of the syphilitic rabbits are so modified that the introduction of an unrelated organism elicits a prompt inflammatory reaction characteristic of the initial syphilitic infection.

Leprosy—Golovine²⁰⁸ is of the opinion that the concurrent existence of infection with syphilis is an important factor in preventing the successful treatment of leprosy. He suggests that treatment of syphilis should be associated with treatment of leprosy in cases in which there is seroresistance.

206 Smith, C. R. Treatment of Syphilis in Tuberculous Patients. Preliminary Report, *Am J Syph, Gonorr & Ven Dis* **22** 72 (Jan.) 1938.

207 Aronson, J. D., and Meranze, D. R. The Effect of Syphilis on Tuberculous Lesions in Rabbits, *Am J Path* **14** 163 (March) 1938.

208 Golovine, S. Essais sur le traitement de cas de lèpre à réaction syphilitique positive, *Bull Soc path exot* **30** 839 (Nov. 10) 1937.

Cysticercosis—Castellani²⁰⁹ describes 3 cases of a condition he believes to be syphilitic and previously undescribed. In 2 of the cases a diagnosis of cysticercosis had been made and in 1 case a diagnosis of trichinosis in the stage of calcification. Numerous small nodules, usually the shape of rice grains, were first observed by the patient under the skin of the extremities. Microscopically the nodules showed mainly fibrous tissue. No spirochetes were revealed with silver stains, but the response to antisyphilitic treatment was prompt in each case.

A Positive Reaction to Serologic Tests for Syphilis in Other Diseases—According to Hazen and his collaborators,²¹⁰ 8 per cent of a group of 266 presumably nonsyphilitic patients with malaria showed a positive reaction to one or more of four standard serologic tests for syphilis. Pistoni²¹¹ found that the Meinelke test gave a positive reaction in only about 5 per cent of his cases of malaria. A complement fixation test, however, gave a positive reaction in from 30 to 48 per cent of the cases of malaria during the attack of fever and in 23 per cent after the fever had terminated.

Ester²¹² studied the behavior of a complement fixation reaction and two flocculation tests in the blood of 10 nonsyphilitic patients after the induction of benign tertian malaria. In 8 of the 10 cases the complement fixation test reaction became positive during the febrile periods but reversed to negative after the administration of quinine. One flocculation test gave negative reactions throughout, with the other, four doubtful reactions developed during the febrile period.

Bernstein²¹³ records the finding of a transitory positive reaction to serologic tests for syphilis in 6 of 37 cases of infectious mononucleosis. During the acute stage of the disease the complement fixation reaction and the flocculation test or both gave positive reactions with high titers but promptly reversed. The reversion was so prompt that the author postulates that if all patients had been tested early and repeatedly in the course of the disease, a much higher percentage of positive reactions

209 Castellani, A. Luetic Pseudo-Cysticercosis, *J Trop Med* **40** 232 (Oct) 1937

210 Hazen, H. H., Sencar, F. E., Parran, T., Sanford, A. H., Simpson, W. M., and Vonderlehr, R. A. Serologic Evidence of Syphilis in Malarial Patients, *Arch Dermat & Syph* **37** 431 (March) 1938

211 Pistoni, F. Diagnostic Value of the Wassermann, Meinelke, and Citochol Reactions in Malarial Counties, *Arch ital di sc med colon* **16** 610 (Oct) 1937

212 Ester, F. Sul comportamento di alcune sieroreazioni della sifilide sul siero di sangue dei non leutici inoculati sperimentalmente con malaria terzana benigna, *Gior di batteriol e immunol* **17** 502 (Oct) 1936. Padget and Moore^{1c}

213 Bernstein, A. False Positive Wassermann Reactions in Infectious Mononucleosis, *Am J M Sc* **196** 79 (July) 1938

would have been obtained. These positive reactions were independent of the presence of sheep cells antibodies (a positive reaction to the Paul-Bunnell test) in the patient's serum. Bernstein believes that the positive reactions to these tests indicate, as does the occasional occurrences of miscellaneous bacterial antibodies, the versatility of antibody responses in cases of infectious mononucleosis.

Hatz²¹⁴ reports the case of a white man 41 years of age with infectious mononucleosis of the febrile type who showed a positive reaction to the Paul-Bunnell test and to the Wassermann test. The Kline test, however, gave a negative reaction. When the patient was recovering the Paul-Bunnell and Wassermann tests gave negative reactions.

214 Hatz, B. The Wassermann Reaction in Infectious Mononucleosis, *Am J Clin Path* 8:39 (Jan) 1938.

Book Reviews

Life, Heat, and Altitude Physiological Effects of Hot Climates and Great Heights By David Bruce Dill Price, \$2 50 Pp 211 London Oxford University Press, 1938

This is an extremely interesting synthesis of some of the investigations of the workers in the "fatigue laboratory" of Harvard University. The physiologic adaptations of man to great heat and high altitudes are presented in detail and are contrasted to the biologic adaptations of animal species either native to or successfully introduced into such regions. The modern views of energy exchange serve as an introduction and background to the main portion of the book. The central idea that adaptability depends on the success of the circulatory and respiratory systems in supplying oxygen to the tissues is illustrated by the maximal abilities of the organism, as displayed by trained athletes. Their finest subject in this respect was able to deliver to his tissues 5.35 liters of oxygen per minute at a cardiac output of 35 liters per minute!

Studies in the desert demonstrated that successful adaptation consists in (1) the ability of the sweat glands to "learn" to secrete enough water to cool the body, (2) the ability of the sweat glands to "learn" to secrete this water with minimal amounts of chloride (to conserve extracellular water and prevent depletion of serum chloride), (3) the ability of the circulation to supply enough blood to the periphery to be cooled and (4) successful integration of items 2 and 3 to permit a maximum loss of heat with a minimum rise in the general body temperature. Of the desert animals studied, the burro was best adapted to the environment. It secretes sweat that is almost devoid of chloride, and the water loss of the body is derived about equally from extracellular and cellular sources. (Although Dill does not mention it—these studies indicate why patients with adrenal insufficiency whose kidneys do not retain chloride are in double jeopardy when exposed to hot weather or when placed in situations which induce sweating—as under anesthesia.) It is curious that man and the burro, neither being voluntary inhabitants of desert regions, are better able to live and exercise in extreme heat than are the natural residents. Reptiles and the few birds and small animals that live there avoid the heat of the day by staying in holes, reptiles are apparently successful only because of their extraordinary internal economy of water.

At high altitudes man does not fare as well as some of the animal species. Man's early adaptation to the diminished oxygen partial pressure is threefold. 1 The amount of circulating hemoglobin increases. 2 The respiratory volume and the cardiac output increase. 3 The total base of the blood increases, favoring dissociation of oxyhemoglobin in the tissues. The well adapted natives working in the high Andean mines have a conspicuously lower alveolar carbon dioxide tension than newcomers or persons who cannot stand the altitude. The llamas, alpacas and vicuñas live successfully in the mountains because of the greater affinity for oxygen displayed by their hemoglobin and because of the greater concentration of hemoglobin in their erythrocytes. This is a species characteristic, a true biologic adaptation which is not lost after long residence at sea level. On the other hand, the hemoglobin of the life-long human inhabitants of the heights has no greater affinity for oxygen than has the hemoglobin of dwellers at sea level.

This is a book that Claude Bernard would have enjoyed and is a worthy successor to similar classic studies of Barcroft and Henderson.

Artificial Fever Produced by Physical Means Its Development and Application By Clarence A. Neymann, M.D., F.R.S.M. Price, \$6 Pp 294, with 21 tables and 68 illustrations Springfield, Ill. Charles C. Thomas, Publisher, 1938

This textbook deals with the treatment of disease with physically induced fever. Starting with a history of the subject, chapters are included on the basic principles and the physiology of hyperpyrexia and on the technic of application. The use of hyperpyrexia in various diseases is described. There is a careful discussion, under separate chapter headings, of the treatment by means of fever therapy of the following diseases: dementia paralytica, syphilis of the central nervous system, primary and secondary syphilis, multiple sclerosis, chorea minor, arthritis, gonorrhea and asthma.

The author has given a concise and positive exposition, setting forth in a justifiably enthusiastic manner the excellent results to be obtained by this procedure. He has been somewhat too favorably disposed toward the production of fever by electromagnetic induction as compared to other equally acceptable methods of producing fever.

Neymann's advocacy of the use of ice water sponges to lower an exceptionally high temperature may be criticized. It is generally considered that tepid sponging of the body and the use of an electric fan permit much more rapid lowering of bodily temperature by heat radiation and evaporation, whereas ice water sponges tend to contract the peripheral capillaries and prevent the radiation of heat.

Despite these minor criticisms of the book, the reader will find that it is a scholarly presentation in which all the literature on the subject has been carefully reviewed. This book, although somewhat dogmatic, contains a great deal of valuable information. There is an excellent bibliography, and each phase of the subject is dealt with carefully and completely. It is recommended to all physicians who may be interested in fever therapy or in the various diseases which may be treated by this procedure.

Anales de la Facultad de ciencias medicas de La Plata, Universidad nacional de La Plata, Volume 1 Buenos Aires, 1937

This volume is the first to be published by the National University of La Plata, in Argentina. The purpose of the publication is to present representative and worthy clinical and experimental investigations of the members of the university faculty.

In this first volume are twenty-nine articles on various subjects, including erysipelas, syphilis, osteomyelitis, amebiasis, peptic ulcer, fracture of the neck of the femur and meningitis. Most of the observations represent clinical and therapeutic investigative phases.

Because of the current discussion on the value of conservative therapy in osteomyelitis, the three articles in this issue are worthy of comment. Rodriguez concludes from his study of 26 cases that the Orr treatment is of greatest value. Professor Valls' comments are rather pessimistic. He agrees with Rodriguez regarding the Orr treatment but would limit its use to the chronic conditions. In one article he states that diaphyseal resection gave poor results, and in a later article in the volume discusses 5 cases in which this treatment gave excellent results.

Rossi reports a case of celiac disease in which large quantities of fungi, identified as *Monilia albicans*, were present in the stools. The author makes the suggestion that a systematic search for fungus should be made in this condition.

An excellent review of intestinal amebiasis is presented by Greenway. He reports an analysis of 2,700 cases and concludes that emetine hydrochloride is the most potent therapeutic agent, with chiniofon as an important adjuvant.

The Diagnosis and Treatment of Sexual Disorders in the Male and Female, Including Sterility and Impotence By Max Huhner, M D
Price, \$5 Pp 490, with illustrations Philadelphia F A Davis Company, 1937

In this book the author has combined his knowledge gained from many years of study and experience with facts and ideas combed from the extensive literature to produce a work which constitutes a very usable text and reference book on sexual disorders. He has the entire field divided into suitable sections, and each topic is discussed separately so that readers who are interested in only one topic need not refer to other chapters. The bibliography, which is very inclusive and is a distinct part of the work, will be of great value to those especially interested in this subject.

The author brings out the fact very well that although some sexual disorders may be purely neurologic and others may be due purely to a local pathologic condition in the sex organs, many are a combination of the two conditions and treatment of the psychic alone or of the physical factors alone will not produce results.

The section on sterility and the section on impotence are well handled and well worth studying. The author sometimes favors his own opinions a bit strongly, but his experience will be of value to most readers. This book will be a valuable adjunct to the library of any urologist or gynecologist and to those neurologists who see and treat patients with sexual neuroses. The fact that throughout the work special emphasis is laid on treatment makes it of most practical value.

Clinical Reviews of the Pittsburgh Diagnostic Clinic Edited by H M Margolis, M D Price, \$5.50 Pp 552, with 11 illustrations New York, Paul B Hoeber, Inc., 1937

New ventures in medical publications always are of interest. Here is one worth bowing to.

Several years ago the Pittsburgh Diagnostic Clinic began the publication of a series of reviews on selected medical subjects apparently with the idea of equipping the general practitioner from time to time with short, readable abstracts and, as the editor says, of presenting new guide-posts in modern medical diagnosis and treatment through brief expositions of currently accepted views. These reviews now have been brought up to date and assembled in book form.

The reviews are unpretentious and clearly written, and they cover a wide territory. Diabetes, endocrinology, hematology, cardiology and gastro-enterology—to mention a few titles haphazardly selected from the table of contents—receive consideration in the present volume. The subject of each review is discussed simply. The sentences are short. The current literature is woven into the body of each chapter so that it becomes, as it properly should, an integral part of what is written. At the end of each essay, however, is an admirably well chosen list of bibliographic references, arranged alphabetically, giving not only the name of the author and the name of the journal or the title of the book to which reference is made, but the title of the paper or chapter also. Thus, the reader who wishes to go further can do so easily. The volume as a whole is well executed, it creates a good impression. May future numbers of these reviews be equally attractive!

Lane Medical Lectures. The Mechanism of Heat Loss and Temperature Regulation By Eugene F Du Bois, M D, Stanford University Publications, University Series, Medical Sciences, Vol 3, No 4 Price, \$2.25 Pp 95, with illustrations Stanford University, Calif Stanford University Press, 1937

The lectures on the mechanism of heat loss and temperature regulation by Du Bois include mainly the work which he and his associates have performed

in the Russell Sage Institute of Pathology during the past twenty-three years. The work is presented in physiologic rather than chronologic order of appearance in the medical literature. This extremely important work, which has gained much momentum during the last few years, is correlated with the observations of others. The material is presented under five headings: (1) heat production and heat loss, (2) radiation, convection and evaporation, (3) the significance of the surface area of the body, (4) regulation of body temperature and (5) chills and fever.

The lectures are very instructive and decidedly interesting and are more than worth the time required to read them. They are packed with valuable, first hand information, which is presented in a simple, concise and readily understandable style and which is made most readable by flashes of dry wit interspersed here and there. The reviewer recommends these lectures to all physicians, whether interested in research or solely in clinical medicine.

Clinical Urinalysis and Its Interpretation By Robert A. Kilduffe, M.D., F.A.S.C.P. Price, \$4. Pp. 428, with 40 illustrations. Philadelphia: F. A. Davis Company, 1937.

This book was primarily written for the clinician for use in his office laboratory. The subject matter is divided into three parts. Part 1 contains a history of urinalysis, a description of the anatomy and function of the kidney and a tabulation of the constituents of normal urine. Part 2, the main part of the book, deals with clinical urinalysis and its interpretation. The subject is covered in great detail. Methods, normal variations in tests and the clinical significance of abnormal values are discussed. In most cases several methods for a particular determination are given. For the qualitative estimation of albumin, only the heat and acid test and the sulfosalicylic acid test are described. The nitric acid and Robert's ring tests are considered too delicate for clinical purposes. The chapters on bacteriologic examination of the urine and urinary gravel and calculi should be of special interest to the urologist. Part 3 contains chapters on equipment of the office laboratory, formulas for test solutions and reagents and miscellaneous tables.

Chiefly to recommend this book are the many simple details often omitted from the average book on clinical laboratory methods. The book is easy to read and should be useful in the office laboratory of the clinician and in the office of the physician called on to perform urinalyses for insurance companies.

Nogle undersøgelser over den biologiske virkning og standardiseringen af det antihaemorrhagiske vitamin K By Fritz Schønheyder. Paper. Pp. 143, with 14 figures and an English summary. Copenhagen: Nyt Nordisk Forlag, Arnold Busck, 1936.

The work reported in this dissertation was done in collaboration with Henrik Dam at the Biochemical Institute of the University of Copenhagen and concerns the biologic action and standardization of the new antihemorrhagic vitamin K. At present the only species in which this substance is known to be necessary for life is the chicken. Avitaminosis K is marked by hemorrhages in various parts of the body, especially the breast, legs, gizzard and liver. The coagulation time is strikingly prolonged, and the bleeding results finally in anemia, but the author presents evidence that the hemorrhagic diathesis is not comparable to hemophilia in man and that the anemia is secondary to the hemorrhages.

The substance which prevents or cures this state, as the case may be, is a fat-soluble, nonsaponifiable, thermostable material which is not a sterol and which is not identical with any previously known vitamin. It is found in hempseed, cabbage and tomatoes, the quantities needed for chemical work are best extracted from pig liver. The method of standardization depends on the quantitative use of data on coagulation time and is described on page 137 of the English summary. Both the work and the manner in which it is reported conform to commendably high standards.

Die Zuverlässigkeit der Röntgendiagnostik, besonders Hinsichtlich des Wertes der Urographie, und die Prognose bei Nieren und Harnleitersteinen Acta radiologica, supplement 32 By Helge B Wulff Price, 15 kronor Pp 301, with 36 illustrations Stockholm Håkan Ohlssons Boktryckeri, 1936

This study consists of an elaborate analysis of over 1,000 cases of renal and ureteral stones, representing all the cases of this type noted in the Lund Clinic since 1923 It is therefore of particular interest to the urologist The first important problem is the evaluation of the reliability of roentgenographic diagnosis The introduction of the use of opaque mediums is shown to have improved the results materially Examination in the presence of pain as compared with examination during the period in which there is no pain also shows interesting differences The second main aspect of the study deals with prognosis and with conservative and operative methods Definite differences, for example, as regards recurrences, are brought out

The work is thoroughly done The large group of cases adds considerable weight to the conclusions, which in a statistical study lean heavily on numbers However, the space occupied appears to be considerably more than is justified or necessary for a study of this type For example, 1,085 brief case reports are given Actual publication of these notes adds little to the interpretations of the paper, yet they occupy 110 pages

Diagnosis and Non-Operative Treatment of the Diseases of the Colon and Rectum By Gottwald Schwarz, M D, Head of the X-Ray Department, Kaiserin Elizabeth Hospital, Vienna, Jacques Goldberger, M D, Consulting Physician of Carlsbad, and Charles Crocker, M D, of New York Price, \$10.50 Pp 540, with 246 illustrations and 9 colored plates New York Paul B Hoeber, Inc, 1937

This book appears to be a translation into English of a monograph originally written a few years ago in Germany and since brushed up for American consumption It is a good translation and sets forth clearly the recent views that have developed abroad on the diagnosis and nonoperative treatment of diseases of the colon and rectum About 90 per cent of the references cited were published before 1935, so that a little doubt arises as to how much care was taken in assembling the American model However, the printing is clear, and the illustrations are excellent The bibliography, in contrast to the rest of the book, has been carelessly put together and does not follow the style usually adopted by the "better-dressed" medical textbooks

En metode til bestemmelse af menneskets blodmaengde ved hjælp af differantitoksin By Erin Madsen Pp 120, with an English summary Copenhagen Levin & Munksgaard, 1936

The author presents a serologic method for the determination of the blood volume in man by injecting intravenously a known amount of antidiphtheric horse serum The concentration of the diphtheria antitoxin (measured by the intracutaneous method for rabbits) is determined for the plasma obtained from a sample of blood taken five minutes later A mean error in the measurements of the blood volume is claimed to be plus or minus 3.7 per cent Repeated determinations of the blood volume of 25 normal men and 25 normal women were made The blood volume of the men was 755 plus or minus 184 cc per hundred grams of body weight and for the women 685 plus or minus 136 cc The author feels, however, that owing to the large individual variations in blood volume, this method of determining the volume is of very limited clinical usefulness There is an excellent review of the various methods of making determinations The obvious criticism of the author's method is the sensitization of the individual to horse serum

Cytologie du liquide céphalo-rachidien normal chez l'homme By H Jessen
Price, 40 francs Pp 160 Paris Masson & Cie, 1937

This is a monograph on the cerebrospinal fluid, with particular emphasis laid on the cytology. It is a critical monograph as well as a practical treatise. In it are incorporated also the personal observations of the author. In addition to the main data contained in the work there is a very extensive bibliography covering 20 pages, which contains references not only to the French literature but also to a very considerable number of papers by American and English authors. The chief criticism of the book would be that in goodly part it is rather elementary. A great many pages are devoted to information which is available to the student or to the neophyte in the study of the cerebrospinal fluid in textbooks on the subject and which seems unnecessary in a book of this type.

The Fundamentals of Electrocardiographic Interpretation By J Bailey
Carter, M D Price, \$4.50 Pp 326, with 251 illustrations Springfield, Ill
Charles C Thomas, Publisher, 1937

The author presents this book as an aid to the novice in electrocardiography. It is essentially an expansion of his series of articles which appeared in *The Journal of the American Medical Association* in 1932. An earnest attempt to present the subject in condensed form is evident, but in places this results in a sketchy presentation of important phases of the work, particularly where graphic and clinical correlations are attempted. This little book without doubt will be helpful to the student, yet it embodies nothing that gives it an advantage over other hitherto published books on electrocardiography.

Sex Life in Marriage By Oliver M Butterfield Cloth Price, \$2 Pp 192
New York Emerson Books, Inc, 1937

Physicians who have not devoted much time or thought to the human perplexities involved in marital relations would do well to prescribe this book for reading by young persons who come to them for counsel before marriage. The author is well qualified as an adviser. He brings to the subject expert knowledge and deep human understanding. The book impresses the reviewer as more practical and useful as a guide to those ignorant of the physical side of marriage than any of the many he has encountered, and its wide distribution undoubtedly would prevent much unnecessary unhappiness.

Synopsis of Digestive Diseases By John L Kantor, M D, Associate in Medicine, Columbia University Price, \$3.50 Pp 302, with 40 illustrations and 7 tables St Louis C V Mosby Company, 1937

This is a convenient little book to slip into one's pocket and to read at odd moments. It represents an honest effort to present simply, clearly and concisely the essential facts concerning the diseases of digestion and appears to accomplish this object in a satisfactory way.

Many compendiums of this general character are poorly written, badly illustrated or so sketchy as to be scarcely worth reading. This synopsis, however, has avoided these pitfalls and is excellent in every way. It should be popular and should have a useful career.

Estudio clinico y terapeutico de las hemorragias graves por ulceras gastro-duodenales By Ignacio Maldonado Allende Pp 148 Cordoba, Argentine National University Press of Cordoba, 1935

This review of the pathologic anatomy of peptic ulcer is rather elementary and below the standards that would be expected of a similar book published in this country. The author devotes considerable space to a discussion of massive hemorrhage, but he does not bring out anything that is new or that is not known by students of gastroenterology.

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